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VITAMIN A DEFICIENCY IN CHILDREN

Part I—Present knowledge of the clinical effects of vitamin A deficiency, with special reference to children

BY

HELEN M. M. MACKAY, M.D., M.R.C.P.*
(From the Queen's Hospital for Children, London.)

An experimental investigation, undertaken by the author at the Queen's Hospital for Children in London (see Part II of this report), suggested that artificial feeding of a type frequently given to infants in this country may not provide sufficient vitamin A for their needs, and that the earliest symptoms of this deficiency in babies may be an increased susceptibility to minor infections of the skin. Up to the present time, vitamin A deficiency in the human subject appears to have been diagnosed with certainty only when eye symptoms (night blindness, xerophthalmia or keratomalacia) were present, and these are probably by no means the earliest effects of such a deficiency. The author can claim little first-hand knowledge of the effects of established vitamin A deficiency, but it should be useful to try and construct a clinical account of the disease in children by collating the records of different observers. Such an attempt, however, is complicated by the frequent co-existence of other diseases.

Severe grades of the disease are common at the present time in certain parts of the world, and the author's investigation on babies suggests that slight grades of vitamin A deficiency may be common in Great Britain. Moreover, G. A. Dawson[18], medical officer of health for Darlington, found during a survey in 1928-29, that there were approximately 100 cases of night blindness and xerophthalmia attending nursery and elementary schools in his area. Is this disease equally common, but passing unrecognised, in other distressed areas of Great Britain and the western world?

Clinical studies concerned with vitamin A can be roughly divided into three groups: 1. Studies of cases of night blindness, xerophthalmia and keratomalacia and their response to treatment; 2. Studies of the effect of administering vitamin A to groups of individuals, either as a prophlyactic measure or in the course of acute infections; and 3. Estimations of the amount of vitamin A found in human organs under different conditions.

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* Working as a member of the scientific staff of the Medical Research Council.

Part II entitled 'Vitamin A Requirements of Babies: Skin Lesions and Vitamin A Deficiency' will appear in the next issue.

The ophthalmic symptoms and signs of vitamin A deficiency have been frequently described, but in this paper attention will be concentrated on the less well-known changes observed in other parts of the body. No attempt will be made to summarize the mass of work carried out on animals on the subject of vitamin A deficiency.

For those who wish to pursue the matter further, a very useful paper by Eusterman and Wilbur[24] with a fairly extensive bibliography on vitamin A deficiency in man appeared in 1932, and Blegvad's paper[5] in 1924 gave a large number of references to the literature of xerophthalmia and keratomalacia Among older papers those of Stephenson[94, 95], published in 1898 and 1910, gave valuable bibliographies.

Effects of vitamin A deficiency in animals.—Before considering vitamin A deficiency in the human subject, the disease in the rat is worth recalling. This vitamin is stored by the rat mainly in the liver, and the rapidity of onset of symptoms on a vitamin A deficient diet varies with the amount of this store and the age of the rat. In young rats the diet of the mother may influence the amount stored in the young, and hence their resistance to a deficient diet[62]. Deficient growth, or arrested growth, followed by loss in weight, are perhaps the symptoms most often stressed in the literature. Eye changes are usually a marked feature. Their appearance often coincides with cessation of growth, but may occasionally precede it, or may not develop at all[89], hence the stage of the disease at which xerophthalmia develops is very variable. Its incidence in rats suffering from gross deficiency of vitamin A varies widely, say from 98 per cent. in Emmett's records[23] to 38 per cent. in Green and Mellanby's[33], presumably depending on the diet employed and the age of the rat[89]. The eye symptoms are in part the direct result of deficiency, and in part due to superadded infection; the first symptom is often puffiness of the lids with conjunctivitis, followed later by purulent and haemorrhagic discharge[89], and opacity of the cornea[37]. As regards the skin changes, there is striking evidence of 'cutaneous malnutrition,' which is said by Steenbock, Sell and Buell[93] to be more common in rats over 4 months old. This shows itself in scabbiness of the tail or ears, sores which heal with difficulty on the nose and feet, and thin and bushy hair. Gudjónsson[37] states that the earliest change in the rat is in its hairy coat, and that changes in the texture of the skin, loss of agility, and a hoarse voice all precede the eye changes. Tyson and Smith[102] found that epithelial hyperplasia of the tongue was regularly present before xerophthalmia. Nasal discharge, sneezing and coughing often occur in the early stages of the disease[93], and diarrhoea is common[89]. Priapism is said to be common in males[37], and inflamed glands and abscesses may appear in the neck. Rapid loss of weight, probably accelerated by infections, occurs terminally.

The symptoms of vitamin A deficiency, however, vary in different species of animals. For example, xerophthalmia is apparently not a prominent symptom in monkeys or in guinea pigs. In monkeys it would seem that gastro-intestinal symptoms and loss of weight are the outstanding features[100, 101]. Tilden and Miller[100] state that out of 11 monkeys dying as a result of vitamin A deficient diets, none had xerophthalmia, though post mortem 9 showed in other parts of the body the epithelial changes typical of vitamin A deficiency. These monkeys showed no special susceptibility to infections of the respiratory tract. In guinea pigs the chief signs of vitamin A deficiency during life are said by Wolbach and Howe[106] to be loss of weight, with desiccation and often necrosis of the margins of the pinnae of the ears, but without eye changes—although post mortem extensive epithelial changes are found in various parts of the body. Hence in different species of animals it seems that different groups of symptoms predominate, and for this reason alone it is not possible to determine from animal work what will be the exact clinical picture of vitamin A deficiency in man.

The post-mortem changes are, however, illuminating and similar changes are found both in man and in animals. The characteristic changes due to vitamin A deficiency are alterations in epithelial structures. This apparently holds true for all the different species investigated post mortem. S. Mori in 1922[75] first described these changes in the larynx, trachea and in ducts of various glands of the rat. Wolbach and Howe[106] showed similar changes in other parts of the body. The normal columnar or cuboidal epithelium is changed to epithelium of a stratified, keratinized type in many parts of the body, including eyes, air passages, alimentary tract, renal tract, and salivary and other glands. It seems that this alteration in and keratinization of epithelium precedes, and is the direct cause of, the many local infections found in rats dying of vitamin A deficiency (see Wolbach and Howe[107], Cramer[15], Harris, Innes and Griffiths[38]).

Thatcher and Sure[99], working with white rats on a diet deficient in vitamin A, found that there might be metaplasic changes in the posterior part of the tongue, in the salivary glands, in the respiratory and in the urinary tract, before there had been any external signs or symptoms.

Immunological reactions, it is held, have not indicated a reduction in general immunity (see Zilva[111], Cramer and Kingsbury[16], Harris, Innes and Griffiths[38]), though on the other hand to what extent reduced resistance to infection is commonly reflected in the known immunological reactions seems a moot point.

The sequence of events in vitamin A deficiency appears to be that patches of keratinization of epithelium develop simultaneously in different parts of the body, and at various sites the altered epithelium allows organisms to gain entrance, and these set up localized abscesses and other inflammatory changes. The proportion of infections occurring at different sites seems to have varied in different laboratories, but Green and Mellanby's figures[33] seem fairly typical. Post-mortem examinations of 92 rats on vitamin A deficient diets revealed an abscess at the base of the tongue (probably originating in salivary glands) in 72 per cent.; middle ear abscess and septic nasal sinuses in 20 per cent.; genito-urinary infections or calculi in 44 per cent. and lung infections in 9 per cent.

Mellanby[67] has carried out on animals work demonstrating the experimental production and prevention of degeneration of the spinal cord; for instance dogs getting ergot in their diet which was deficient in vitamin A developed demyelination of the cord, whereas if the diet was not deficient in vitamin A these changes were prevented. It seems possible that vitamin A deficiency may play a part in the etiology of certain diseases of the central nervous system in man, but as the main purpose of this paper is to give an account of vitamin A deficiency alone, and the clinical implications of Mellanby's investigations are not yet clear, this important work is not further considered.

Studies of night blindness and keratomalacia in man.

Geographical distribution of vitamin A deficiency in man.—To ascertain the distribution of proved cases of vitamin A deficiency, we must examine the records of acquired night blindness, of xerophthalmia and of keratomalacia.

Nearly all observers agree that young children develop symptoms of vitamin A deficiency more readily and suffer more severely than older persons; though naturally night blindness (the earliest eye symptom) is unlikely to be detected in an infant or very young child. Hence wherever the disease is reported among adults, it is likely also to be present among children.

That it has been, and still is, common in certain parts of the world, is clearly shown by the widespread popular knowledge of the means of cure, such knowledge dating apparently from very ancient times. Liver therapy was advised for night blindness, so Blegvad[5] states, in a papyrus of about 1500 B.C., and also by Hippocrates in the fourth or fifth century B.C., and it is still employed by the people in Russia[66], in Labrador and Newfoundland[1], in India[113], and in China[58], though in Tientsin it is said that the Chinese frequently treat the wrong eye diseases with liver: and liver may be mistakenly used in this disease as an external application to the eye instead of being taken internally, as was noted by de Gouvêa in Brazil in 1883[19]. In Japan the popular remedy since olden times has been, according to S. Mori[75] writing in 1904, a fish rich in fat, and fowls' livers are also used[5].

During the nineteenth century it was probably a fairly common disease in many European countries as well as in America and in Asia. Stephenson[95] gives to Joseph Brown the credit for the first clear clinical description of keratomalacia which he described in the Edinburgh Journal of Medical Science of 1827, and also notes that thirteen years later, in 1840, William Mackenzie said he had repeatedly seen keratomalacia in this country in emaciated infants with diarrhoea. In 1876 in Sheffield, Snell[91] was successfully treating with cod-liver oil and iron children who suffered from night blindness and Bitôt's spots. The disease was described by many German writers, and in Berlin in 1866 von Graefe said that he sometimes saw 3 to 4 cases of keratomalacia a month[95]. It was also reported from France and Russia; for example Bitôt[4], whose name has been attached since 1863 to a characteristic appearance in the eye, was a French physician in Bordeaux, and Blessig[6], writing from Petrograd about the same time, remarked on its occurrence in Russia, especially during the Lenten fasts. Many outbreaks in prisons, workhouses, schools and asylums were reported in various countries, as Blegvad[5] has noted. In this country Stephenson's figures[94] show that at the end of the last century xerophthalmia was present in nearly all the poor law and industrial schools and orphanages where he examined the children. Out of 6,209 school children examined by him, 116 or 1·87 per cent., were suffering from xerosis of the conjunctiva. The frequency of keratomalacia in some parts of India at the end of the last century is shown by the fact that Herbert[39] in Bombay was able to collect 100 cases in 4 months. Turning to America we are told that the disease was common 40 to 50 years ago among negro slave children in Brazil[19] and in South Carolina[50].

It appears that in recent years xerophthalmia is still common in many countries. In China and Japan, Pillat[78, 79] reports that the disease is widespread and common, and Lossouarn[58] says that at an eye clinic in Tientsin in 1929-30 one in every seventeen patients was suffering from xerosis of the conjunctiva. In India, Kirkpatrick[49] finds that the children's ward at the Madras Government Ophthalmic Hospital is rarely without a case of keratomalacia, though it is commonest in times of scarcity. Wright[111] states that it is the commonest cause of preventable blindness in India at the present time, a statement in which the professors of ophthalmology in Calcutta, Bombay and Lucknow apparently concur. In Yucatan in Central America Carillo[12] writes of xerophthalmia as a common deficiency disease in 1932, and Aykroyd[1] finds a large percentage of the population of Labrador suffering from night blindness. Severe outbreaks of the disease have been reported recently from prisons in Uganda[71]. During the time of privation following the Great War, and during the War, children with xerophthalmia and keratomalacia were seen in many clinics in Austria and in Germany; for example, Gralka[32] says that at the Breslau Kinderklinik in 1922 he saw 30 cases of keratomalicia, whereas at the same clinic between 1912 and 1921 there were only 6 cases. Austrian physicians reported that during the War night blindness was common among prisoners of war in Russia, and occurred also among the peasants[66]. Non-belligerent countries did not escape either, and in Denmark, Blegvad, writing in 1924, had collected 582 cases occurring between 1909 and 1920, and it is said that vitamin A deficiency is now the commonest cause of blindness in that country.

Lastly, let us consider some records from our own country during the present century. In 1910 Stephenson[95] described 31 cases of keratomalacia in infants, most of which he had seen in the space of a few years at the Queen's Hospital for Children and at the Evelina Hospital, both in London. In contrast to this, during the last 12 years, the author, also working at the Queen's Hospital in what is still a very poor district, has seen no keratomalacia and only one case of xerosis of the conjunctiva. Hence in spite of the poverty prevalent nowadays, both the standard of living and the care of infants has improved sufficiently in the last quarter century to make gross A deficiency as evidenced by keratomalacia a rare condition in London. The provision of a milk grant for young children of impoverished families probably plays a very important part in this improvement. It has, however, been suggested that certain outbreaks of eye symptoms and 'distorted pneumonia' in industrial schools during the present century have resulted from vitamin A deficiency[63]. In this country, it seems probable to the author that owing to the medical care bestowed on infants, eye symptoms, should they occur, are more likely to be found in older children as xerosis of the conjunctiva. This seems to be borne out by the following records:—

> In 1921 Dr. Tyrrell, one of the Assistant School Medical Officers for the West Riding of Yorkshire, in his Annual Report, cited 19 cases of night blindness and dryness of the conjunctiva discovered in the Doncaster area after the coal strike of 1921. Under treatment with a diet containing milk, eggs, butter, green vegetables and fruit, the night blindness was cured in four to six weeks, and the dryness of the conjunctiva in two to three months (personal communication from Dame Janet Campbell, Ministry of Health). In 1928-29 G. A. Dawson[18], medical officer of health for Darlington, after seeing cases of xerosis of the conjunctiva in children admitted to the local fever hospital, carried out an investigation and found approximately 100 cases among children then attending nursery and elementary schools in his area. The diagnosis was confirmed by A. T. Paterson. Spence[92], in Newcastle-on-Tyne, has been able to collect 17 cases of xerophthalmia and night blindness in one year, 11 of these being children under 15 years old; but he saw no babies suffering from the disease.

If individual investigators are able to find as many cases as this in one district, or attending one hospital, it seems probable that considerable numbers exist in other distressed areas of the country at the present time, and one wonders whether in this country, as a whole, eye changes due to vitamin A deficiency are not more common than the paucity of records would lead one to suppose. The author's work at the Queen's Hospital for Children strongly suggests that slight vitamin A deficiency, insufficient in grade to produce eye changes, is common among infants, but these cases are in no way comparable to the cases of keratomalacia and xerophthalmia which have been under consideration.

Seasonal incidence of xerophthalmia and keratomalacia.—A seasonal incidence has been noted in many parts of the world. M. Mori[74] found the disease developing in Japan in the 'diarrhoea months,' i.e., July to September, the slighter cases undergoing spontaneous cure in late autumn and winter, and perhaps relapsing again next year. Stephenson[95], in this country, also found that keratomalacia was a disease of the diarrhoea season (summer), and that xerosis in school children developed during the spring and summer. He considered the increased exposure to light in the summer an important aetiological factor[91]. On the other hand, the Danish cases developed chiefly between December and May, with a peak at the end of winter about March or April; the fall in incidence corresponding closely with the date when stall-fed cows were driven out to grass[5]. Gralka[32], in Germany, found a similar seasonal distribution. Small epidemics among Japanese workmen in Manchuria were at their height in February and March, and this was attributed to the scarcity and high price of fish in these months (Mori quoted by Medical Research Council[66]). It seems, therefore, that the seasonal incidence varies with local conditions; any local condition tending to a decrease in the vitamin A content of the diet at a given season no doubt affecting the incidence.

Age incidence of xerophthalmia and keratomalacia.—Eye changes due to vitamin A deficiency may occur at all ages, and keratomalacia has even been recorded in an infant at birth[64]. Other factors being equal, young and rapidly growing children are the most likely to show signs of the deficiency, and Blegvad[5] brings out clearly the greater rapidity of the illness in young infants than in older ones. In descriptions of outbreaks of keratomalacia (that is the advanced stage of the eye changes) the majority of the children attacked have usually been under 1 year, whereas in descriptions of xerosis of the conjunctiva (which is a relatively slight change) we usually find the greatest incidence in older children.

The age incidence of eye symptoms in any particular area is likely to depend to a great extent on local factors. Thus in Denmark the disease was largely one of bottle-fed babies given skimmed milk[5]; whereas in Japan, where breast feeding was presumably the rule and no cow's milk was available, the disease occurred chiefly after weaning, in children of 2 to 5 years old[74]. Spence's cases[92] in Newcastle varied from 2 to 54 years old; though the majority were children, there were no infants among them, and this may well be accounted for by the milk grant available for infants of the poorest families in this country.

Diets which have caused xerophthalmia and kerotomalacia.—It has long been recognized that xerophthalmia and keratomalacia are diseases of defective nutrition, and likely to occur on diets deficient in animal food (de Gouvêa[19]). Mori[74], about 30 years ago, attributed it to deficient fat. In spite of the widespread and ancient use of liver as a therapeutic agent, however, it is only since animal experiments established the existence of vitamin A that it has been possible to determine the specific cause of this disease.

Xerophthamia and keratomalacia appear only to have been recorded in children living on extremely ill-balanced diets, or in breast-fed babies whose mothers were on such diets. So that in human beings a diet sufficiently lacking in vitamin A to cause xerophthalmia or keratomalacia is usually very deficient in other respects also, and it must be very rare to find a human diet deficient only in vitamin A. Vitamin A is present in full cream milk and milk products, eggs, fat fish and meat fat, green vegetables, carrots, tomatoes and other fruits and vegetables containing carotene. All these foodstuffs usually appear to have been either absent or deficient in the diets of xerophthalmia patients, hence it is not surprising that other deficiency diseases are often reported in association with this condition. The following are some examples of ' xerophthalmia diets ':—

Mori's Japanese cases[74] usually lived on rice, barley and other cereal food, beans and vegetables; Frazier and Hu[28], in China, describe a diet consisting chiefly of rice, maize, millet and occasionally wheat flour with white cabbage and salted vegetables; the diet of Spence's cases[92] in Newcastle consisted chiefly of wheat flour bread (often in very large amounts), margarine, jam, vegetables and tea, with no milk except in in tea, and a few ounces of meat in the week; Dawson's cases[18] were living mainly on white bread, margarine and tea; many of Bloch's Danish cases[7] (for the most part children under 12 months old) had been fed on skimmed milk (pasteurized and reheated), oatmeal gruel and ' barley soup.' Commenting on the dietary of Bloch's cases, McCollum and Simmonds[59] state that when the cereal consumption was large the children would have suffered from a deficiency of inorganic elements, and that the diet was probably on the borderline for rickets, scurvy and beri beri. Bloch's own findings[8] support this statement. He found pronounced evidence of rickets in nearly one third of his cases, scurvy in at least one, and a number with a condition described as ' carbohydrate dystrophy ' with oedema (a condition also noted by Mori in some of his cases and probably the same as the so-called ' war oedema ' or ' hunger oedema ' which may be a protein deficiency). Some of Bloch's cases, like a few others recorded in the literature, suffered from muscular hypertonicity which may have been due to another dietetic deficiency; or possibly Mellanby's work[67] on degeneration of the cord in dogs may throw further light on such cases. Forest and Wolff[26], in Strasburg, observed the development of xerophthalmia in babies fed from an early age as follows: dried skimmed milk 10 per cent.; sugar 5 per cent.; and a preparation of rice 5 per cent.; the calorie allowance was about 120 calories per kilogramme body weight daily. The ration provided about 15·3 centigrammes of fat daily.

Sometimes it is the mother's diet which is grossly ill balanced. Thus Thalberg[98], in 1883, reported a number of cases of keratomalacia in breast-fed babies in Russia, the babies were for the most part very wasted and the majority were children of ill-nourished women who had undergone a religious fast. In the post-war years breast-fed babies with xerophthalmia were reported from Germany by Gralka[32], and Thatcher and Sure[99] have recently reported such cases from America.

Mori[74], in Japan, examined the milk of two mothers whose infants had xerophthalmia and found a fat percentage of 0·14 or less. Thus it is evident that the vitamin A value of human milk may be so low, that, though the child's diet consists wholly of milk, he is not protected from severe deficiency. This variability in the vitamin A value of a given foodstuff must be borne in mind, and such differences may account for some unexpected records. For example eggs are usually rich in this vitamin, and Lossouarn[58], in China, finds eggs a valuable therapeutic agent in this disease, but Spence[92] reports that, according to the histories obtained, two of his patients had had one egg daily for at least four weeks without preventing the onset of eye symptoms. Again the vitamin A value of cow's milk may be largely destroyed by the treatment to which it is subjected: hydrogen peroxide, which has been used as a preservative in some countries, would presumably have this effect. Marshall Findlay, quoted by Cramer[14], belived that he was able to correlate the development of a chronic eye disease and 'distorted pneumonia' in an industrial school in this country in 1919, with destruction of vitamin A by a system of cooking under pressure which reproduced the conditions of an autoclave.

When the dietetic deficiencies are multiple the clinical picture will naturally be mixed, and sometimes one deficiency and sometimes another, may overshadow the rest. Moreover, the symptoms in the mother may be those of a different deficiency to that noted in her infant. Maxwell[64] reports an interesting case from China of a baby born with keratomalacia: the mother's symptoms, however, were not those of vitamin A deficiency but of vitamin D deficiency: she was suffering from osteomalacia. Again, Thalberg[98] found xerophthalmia in the breast-fed infant of a beggar woman with apparently hunger oedema. On the other hand, as would be expected, the babies of women suffering from xerophthalmia may show symptoms of the same disease[39].

It would therefore seem that xerophthalmia and keratomalacia have usually developed on high carbohydrate diets containing little animal fat or green vegetables, and such diets have usually been deficient in other substances besides vitamin A. Nevertheless, it should also be remembered that skimmed-milk feeding has sometimes been the cause of this trouble, and that even breast milk may be sufficiently deficient in vitamin A to cause keratomalacia if the mother has suffered great privation.

Duration of a deficient diet.—The time necessary for the development of xerophthalmia in a child on a deficient diet presumably varies as it does in young rats, and depends on such factors as the store present in the body at the outset, the degree of deficiency in the diet, the age of the child and the rate of growth. According to the observations of Forest and Wolff[26], babies fed from the age of 2½ months or less on a skimmed milk and carbohydrate diet developed xerosis of the conjunctiva 3 to 4 months after starting the diet. Blegvad[5] found that the disease may develop in under 2 months if the baby starts a deficient diet during the first quarter year of life, but that when the child was over 12 months of age the average duration of the deficient diet before the onset of symptoms was 8½ months. His cases were all young children or infants. Herbert[39] says that patients may continue for many years, with intervals, to suffer from xerosis.

Symptoms of vitamin A deficiency in children.—Pillat[79], who has had the opportunity of studying many cases of xerophthalmia, summarizes the effect of vitamin A deficiency as: 'a system disease of the epithelial . . . apparatus of the body,' and states that 'keratomalacia is merely one symptom . . . of a general disease; for the skin, the hair, the nails and the various glands of the body, and the mucous membranes of the respiratory, digestive and urino-genital tracts are all concerned.'

GROWTH, NUTRITION AND GENERAL CONDITION.—Wasting is a prominent feature in most clinical descriptions of children suffering from keratomalacia, but in the majority it is quite impossible to say how far this is attributable to vitamin A deficiency, in view of the miserable diets and coincident illnesses reported. Rapid wasting is apparently more common, as one might expect, in the infant with keratomalacia than in the older child with only xerosis of the conjunctiva. There is some evidence to suggest that loss of weight is a much less dramatic feature of the disease in the relatively slow growing human child than it is in the rapidly growing young rat. For example, Spence[92] states of his 11 cases in children that all but one 'had the appearance of well-nourished active-looking people.' Moreover, the administration of vitamin A and cure of the eye condition did not necessarily result in a coincident rise in weight or height. Stephenson[94] says of his children with xerosis of the conjunctiva that they were usually well nourished, though his standard would appear to have been rather low. Thalberg[98] and others have recorded xerophthalmia in individual instances in children who have looked in good general condition. Aykroyd[1] (probably referring to adults) states that night blindness may occur in persons otherwise apparently in good health. Forest and Wolff[26] in Strasburg, who observed the development of xerophthalmia in babies on a diet of skimmed dried milk and carbohydrate, state that the weight increase on this diet was regular though slow; in the period preceding the development of eye symptoms the average increase was 10 to 15 grammes daily, say $2\frac{1}{3}$ to $3\frac{1}{2}$ ounces weekly, as compared with the normal average of about 6 ounces weekly. As these babies probably also suffered from a deficiency of vitamin D, and possibly also of vitamin C, it is not possible to assess the influence of different factors on their rate of growth. Apparently with the development of eye symptoms the weight became stationary. There is no doubt that ultimately a deficiency of vitamin A, if sufficiently severe and prolonged, must cause wasting and death in children just as in experimental animals, but it is evidently possible for xerophthalmia (like scurvy and rickets) to be present in a child of approximately normal weight and height.

If the child survives the illness, Bloch[8] states that his ultimate growth is not retarded: of 64 blinded children who were examined by him at 12 years old and upwards, few were under standard weight. Possibly if the children had been older when they suffered from vitamin A deficiency and the disease had been of longer standing and more chronic, a different result might have been obtained. The present author's impression is that a child under one year old with active rickets which is diagnosed and adequately treated, will usually show good growth, whereas it is well known that the child stunted with rickets at, say, 3 years old, will probably be well under standard height at 12 years old. Similar findings may well apply to vitamin A deficiency.

Some writers, among them de Gouvêa[19] in 1883, have laid special stress on the apathy, mental dulness, and complete loss of energy and initiative of persons suffering from keratomalacia.

CHANGES IN THE EYES.—To assess the frequency of eye symptoms in persons suffering from vitamin A deficiency is impossible in the present state of our knowledge, since the diagnosis of vitamin A deficiency is usually only established because eye symptoms are present. Night blindness appears invariably to precede any objective eye changes, but in children under 2 years old it is unlikely to be recognized. This no doubt partly accounts for the more advanced stage of the eye disease in most young chidren when treatment is first sought, but it is also clear that the disease is a more rapid one in young children than in older persons, and hence the stage of night blindness without xerosis is probably considerably shorter. Exposure to strong light may precipitate the development of night blindness, a point stressed by Stephenson[94] in 1898 and, even as long ago as 1883 by de Gouvêa, and recently emphasized by Aykroyd[1] in his description of the condition in Labrador. De Gouvêa notes that at dawn the vision is better than in the dusk of evening after exposure to sunshine during the day. Deficiency of vitamin A apparently leads to subnormal formation of visual purple in the retina, and so to night blindness.

The first characteristic objective eye change noticed is usually slight irregular dryness and the appearance of Bitôt's spots, with perhaps shrinking or wrinkling and loss of lustre of the scleral conjunctiva. Bitôt's spots are very characteristic: they are whitish or yellowish foamlike spots on the bulbar conjunctiva, looking as though they would easily brush off with a movement of the lids, but actually remaining unchanged when the lid is gently rubbed over them. In the babies observed by Forest and Wolff[26], Bitôt's spots appeared 10 to 15 days after the first signs of dryness of the conjunctiva. Later corneal changes make their appearance: the cornea loses its lustre and becomes hazy, dull and dry and loses its normal sensitivity, and may show whitish plaques. If the condition continues to progress, the cornea becomes greyish and then necroses. Not infrequently there is superadded infection even before the characteristic changes appear, and an early conjunctivitis may develop together with photophobia. The lids may be swollen in the early stages and blepharitis and styes are common[78]. In the later stages of keratomalacia a hypopyon may develop or the iris prolapse, and finally the whole globe is disorganized, perhaps with panophthalmitis. In the presence of infection the characteristic appearance of the eye may be masked (see Herbert[40]; Stephenson[95]). A marked feature is reduced sensivity of the coverings of the eyeball, and Stephenson draws particular attention to the apparently small amount of pain associated with keratomalacia, and the comparative ease with which the physician can consequently examine the eye, a feature which he says should immediately suggest the nature of the condition. In advanced cases the sensitivity of the cornea may be 100 times below normal, and that of the conjunctiva perhaps 4 times below normal as demonstrated by John[46]. This diminished sensitivity has been found to persist after months of treatment, and long after the xerotic changes have disappeared.

It is of interest that Kreiker[51] has shown that at an early stage of the eye disease, before any macroscopic eye changes have occurred, there are already epithelial changes which can be detected in microscopic sections, and no doubt it is this epithelial change which predisposes to infection.

In the dark skinned and yellow races slaty pigmentation of the conjunctiva may be an early symptom[40], but up to now no such pigmentary change appears to have been reported in white patients[80].

Pillat[79], who gives a full account of these eye changes, states that they can best be studied in adults in whom the disease is less rapid. Because the disease is more severe and more rapid in the infant than in the older child, keratomalacia is most often found in infants, whereas children of school age may suffer for months from night blindness and xerophthalmia without the disease progressing as far as keratomalacia. Hence the younger the child the greater the risk of blindness. If adequate treatment is given in the earlier stages of the disease, the cure of the eye symptoms is rapid and complete; but it is obvious that if the corneal changes are advanced blindness must result. Vitamin A deficiency was recently found to be the commonest cause of blindness in Denmark, and Blegvad[5] stated that only 14 per cent. of the Danish children who survived the disease had fairly good vision. Mori[74] reported that a large number of the children who survived the disease in Japan were blind, and Pillat finds it to be a common cause of blindness in North China. Wright[111], as previously stated, concludes that it is ‘ the chief cause of preventable blindness in the Indian empire.’

CHANGES IN THE SKIN AND HAIR.—Skin symptoms probably precede the eye symptoms in many cases, and this seems of special interest in view of the author's finding regarding the lower incidence of skin infections in babies given a supplement of vitamin A (see Part II). De Gouvêa[19] described in 1883 the dry, scurfy-looking skin with diminished sensitivity, and falling out of the hair often associated with this disease, features mentioned by many subsequent observers as will be seen below. Mori[74] in Japan, Stephenson[95] in England, Bloch[7] in Denmark, Kirkpatrick[49] in India, all were struck with the skin changes, and most of them noted also changes in the hair, including occasional ‘ bleaching.’ Their patients were nearly all children. Pillat[79], describing the disease in adults in China, devoted much attention to the skin, which he describes as becoming greyish and later yellowish, due to an increase in pigment in the basal cell layer of the epidermis[80]. This pigmentary change, like the similar pigmentary change in the conjunctiva, does not appear to have been recorded in members of white races suffering from vitamin A deficiency. In mild cases, he says the skin looks pasty and puffy; in severe cases the fat disappears and the skin become lined and wrinkled. It feels dry, and there is marked reduction in sweating, and comedones may form. In severe cases the skin is covered with scurf and feels as if it had been powdered with flour, and sometimes larger scales form which adhere more firmly. The hair in severe cases becomes dry and dull and falls out, and the nails may be dry and lustreless and even chalky. Frazier and Hu[28] in China state that several weeks before the onset of eye symptoms in their patients (adults), the skin was dry and slightly rough; subsequently ‘ spinous keratinized papules ’ (presumably the ‘ comedones ’ mentioned by Pillat) appeared at the sites of hair follicles on the limbs and trunk; there was an absence of visible sweating and some wrinkling of the skin and dryness of the hair. Most of these general statements are borne out by individual case histories recorded by other observers, who repeatedly note the dryness of the skin.

Two interesting reports concerning skin lesions in this disease have come from East Africa[71, 30]. There were many cases of night blindness and xerophthalmia in a prison in Uganda[71], and 81 prisoners were segregated for observation; of these 71 suffered from night blindness, 45 had xerophthalmia, and 74 an ‘ acne-form eruption.’

No local treatment was given. The diet was unchanged, except that one ounce of cod-liver oil daily was given to each man. After 9 weeks the percentage of cures was:—night blindness 100 per cent.; xerophthalmia 100 per cent.; dermatoses 98·6 per cent. Thus it will be seen that if we accept this eruption as a symptom of vitamin A deficiency, it was much more common, and an earlier manifestation of the disease, than any objective eye change. The dermatosis is described as 'a dryness of the whole skin with the exception of the face, associated with a papular eruption, most apparent on the extensor surfaces. The papules are smooth, black and extremely irritable. Histologically, these papules are found to have as their nucleus an altered pilo-sebaceous follicle, which is sealed with a comedo, and shows more or less evidence of perifolliculitis.' Pustulation was rare. Sequieri[90] shortly afterwards examined patients at a mental hospital with similar eruptions as well as ocular manifestations of vitamin A deficiency. He says of the skin that 'as a rule the lesions are small, some little bigger than the head of a large pin, others about the size of a millet seed. They are in the form of blunt cones, and the lens shows that they are about the orifices of the hair follicles.' He said that he had seen this condition of the skin not infrequently in Kikuyus both on the farms and in hospital.

Besides changes in the texture of the skin, skin infections, often preceding eye symptoms, are recorded and emphasized by many writers. Lesions frequently mentioned are: furunculosis, pyodermia and ulcers, and sometimes impetigo. The following notes give some indication of the observations of different writers:—

Mori[74] says the xerophthalmia is frequently preceded by a long period of skin sepsis with furunculosis and chronic scalp abscesses, Stephenson[95] noted 'acute bedsores' in his babies with keratomalacia and states that four other writers had already drawn attention to them. In school children with xerosis of the eyes, he found[94] relapsing pustular eruptions common. Bloch[8] found pyodermia common, and Pillat[79] records the presence of furunculosis and styes, and describes one case with what he calls 'dermolacia' or 'decaying hollows' in the skin. Frazier and Hu[28] found a marked tendency to pustulation in one third of their cases, and they speak also of ulcers. Spence[92] found the incidence of skin sepsis, including boils and impetigo, high among his cases. Ross[85] and others mention furunculosis. Aykroyd[1] describes the frequency of 'salt water boils' on the wrist and forearms of fishermen on the Labrador coasts where vitamin A deficiency is common. These boils originate from the rubbing of wet garments, but Aykroyd is doubtful whether they are due to a food deficiency, though it is tempting to assume a similar aetiology in these cases and in the infants described in Part II, in whom local irritation of the skin apparently allowed local organisms to set up dermatitis. The rapid improvement in local skin sepsis following cod-liver oil or similar medication is noted by Pillat[79], Frazier and Hu[28], and Spence[92], and the last three writers state that this improvement occurs without any local treatment of the skin lesions. Forest and Wolff[26] state that those babies in their series who developed eczema showed evidence of xerosis more rapidly than those without eczema; in view of other records, it seems fair to assume that this eczema was, at any rate in part, the direct result of vitamin A deficiency. Even Hippocrates apparently mentioned eruptions of boils in connection with night blindness (see Stephenson[94]).

It would seem from these descriptions that there is no one type of skin infection particularly characteristic of vitamin A deficiency, but that a variety of skin infections, often chronic or relapsing in character, may occur. From the investigations described in Part II of this paper it would seem that vitamin A deficiency favours infections with local organisms at any site of skin irritation from external causes.

Changes in the respiratory tract.—Dryness of the mouth and hoarseness (corresponding presumably with the epithelial changes noted in the larynx and trachea of rats by S. Mori[75], and in their tongues by Tyson and Smith[102]), are described as early symptoms of vitamin A deficiency in man by Herbert[39] and by Lossouarn[58]; the latter noted hoarseness in more than half his cases and stated that it often preceded the appearance of night blindness. Pillat[79] also noted some cases with hoarseness which disappeared with improved nourishment. Respiratory infections are common in most of the recorded groups of cases, but here it seems impossible to guess to what extent the bronchitis and pneumonia are attributable to the vitamin A deficiency. In no large group of cases, so far as the writer can ascertain, are we told that the administration of vitamin A exerted any marked effect on the cure of respiratory infections, and the probable influence of other dietetic deficiencies must be borne in mind, since pneumonia is known to be a common terminal infection in many infants in poor general condition. Blegvad[5] found pneumonia to be the commonest cause of death in the Danish infants who were mostly under one year old and suffered from a variety of deficiencies (including iron deficiency and vitamin C deficiency, either of which might increase the incidence of respiratory infections), and he states that of 60 fatal cases, 46 had pneumonia. In Chinese children with xerophthalmia Pillat[79] found pneumonia the second most common cause of death, and drew attention to the presence of 'obstinate bronchitis' with the disease both in adults and children. On the other hand, in some large series, such as M. Mori's[74] in Japan, pneumonia was not recorded as common, though he says that bronchitis was not infrequent. In the description by Wilson and Du Bois[105] of the post-mortem findings in a child dying of xerophthalmia, it is of interest that the respiratory infection present was not the common bronchopneumonia of babies, but bronchiectatic cavities with abscess formation, resulting presumably from local epithelial changes.

Changes in the gastro-intestinal tract.—The great majority of writers who pay attention to the general symptoms associated with xerophthalmia, emphasize diarrhoea as an early symptom, especially in childhood. It is mentioned, for example, by: Thalberg[98], Herbert[39], Mori[74], Stephenson[95], Yarr[112], Monrad[72], Bloch[7], Blegvad[5], Ross[85], Schwartz[86], Pillat[79], Kirkpatrick[49], Lossouarn[58]. It is, moreover, a common cause of death in this condition (Mori[74], Stephenson[95], Blegvad[5], Pillat[79]). Mori[74] points out that the fortuitous presence of diarrhoea might cause the appearance of xerophthalmia in a border-line case as a result of lessened fat absorption. On the other hand, the rapid cure of diarrhoea which he frequently obtained with cod-liver oil, strongly suggests that these intestinal symptoms, like the eye and the skin symptoms, are generally a consequence and not a cause, and were primarily due to the epithelial changes set up by the vitamin A deficiency. The infecting organism would probably in some cases be a local inhabitant of the intestinal tract, and in some a virulent organism gaining entrance from outside, just as happens apparently in other cases of gastro-enteritis in infancy. Pillat[79] drew attention to cases in which typhoid and dysentery preceded the appearance of eye symptoms, and other cases in which no infective origin could be found for the diarrhoea. Like Mori he found that in the latter type the diarrhoea would usually disappear with treatment with animal fat, including cod-liver oil. He states that similar cases of diarrhoea occur in China without eye symptoms, and are probably also due to vitamin A deficiency. He notes that constipation also may sometimes occur with keratomalacia.

Two other symptoms mentioned by Mori[74], which rapidly disappeared when cod-liver oil was given (apparently with no other treatment), were voracious appetite, which he says appears at some stage of the disease in nearly every case, and abdominal distension. In later stages, however, the appetite might be poor. De Gouvêa[19] and Stephenson[95] were also impressed with the voracious appetite. One is naturally inclined to attribute these two symptoms to a deficiency made good by the oil, and as voracious appetite is not a symptom of rickets, vitamin A deficiency would seem the probable cause. As against this, is the fact that many writers associate poor appetite with xerophthalmia. It is interesting in this connection to recall certain symptoms in a group of kittens fed by the present author[60] on skimmed milk, vegetable oil, orange juice and marmite, and suffering presumably from vitamin A deficiency. These animals showed ballooning of the abdomen and great eagerness for food, beginning all meals with apparently voracious hunger, though the actual intake of food (which was provided ad libitum) was small. This eagerness for food, but small intake, may explain the fact that some writers stress voracious appetite and some poor appetite in children.

CHANGES IN THE URINARY TRACT.—Leber[54] in 1883 described in a post-mortem case desquamation of renal epithelium corresponding to the epithelial desquamation found in the eye with xerophthalmia. Such desquamation shows itself in life, and the presence of large quantities of desquamated epithelium in the urine is emphasized by Herbert[40a] as occurring ‘ in every severe case ’ he had seen. He found it was often accompanied by pus cells in the urine. Spence[92], in his series, found the same condition in ‘ the more severe cases,’ and it persisted till vitamin A treatment was given. Pillat[79] mentions it in one case. Bloch[8] found pyelitis in 27 out of 86 children with xerophthalmia, but is unable to provide information concerning the presence of desquamated epithelium in his cases.

As yet there appears to be no clear evidence showing that renal calculi in man may be the result of vitamin A deficiency, though this has been suggested as a possible cause of such calculi in India.

PYREXIA.—In many cases of vitamin A deficiency, pyrexia occurs which is apparently not due to the presence of infection. De Gouvêa[19] noted this pyrexia in 1883 and Herbert[39], Mori[74], Hsu[43], and Wright[110] have all recorded it as frequent. Forest and Wolff[26] say the pyrexia does not appear until after the onset of eye symptoms. Pillat[79] said he had observed pyrexia associated with diminished sweating, and in 6 severe cases of adult keratomalacia he found that this disappeared with a few days cod-liver oil treatment. Temporarily after the institution of such treatment, there might even be excessive sweating. It seems probable, therefore, that in some cases at least the pyrexia is the result of diminished heat loss associated with the skin changes.

SUSCEPTIBILITY TO INFECTION.—Some mention of infection associated with vitamin A deficiency has already been made. In most clinical accounts of xerophthalmia one is struck by the associated infections. Thus Bloch[8] found in his series of 86 infants and young children that 80 per cent. suffered from an infection: 12 had bronchitis, 15 pneumonia, 13 otitis media, 27 pyelitis and 14 pyodermia. The direct association between vitamin A deficiency and skin infections has already been discussed; what of the other infections? Bloch contrasts his xerophthalmia cases with a series of 32 scorbutic children, with 30 per cent. showing infections, as against 80 per cent. in the xerophthalmia series. But the comparison does not seem fair since vitamin C deficiency is often an isolated deficiency in an otherwise adequate diet, and may occur in the diet of an artificially-fed baby of parents in comfortable circumstances, whereas Bloch's cases of vitamin A deficiency occurred in babies and young children of the poorest classes and the diets were obviously deficient in a number of constituents. Hence it is impossible to determine whether the associated infections were the result of vitamin A deficiency or whether a number of different dietetic defects all played their part.

A contrasting, though very much smaller, group of cases are those studied by Spence[92] in Newcastle. These were older, varying from 2 years to 54 years old, and Spence found, apart from skin infections, no evidence of increased incidence of infective disease among them, or among other members of their families who were presumably for the most part also consuming inadequate diets. Moreover, there seems no evidence in the published descriptions of xerophthalmia to show that vitamin A deficiency predisposes to any of the infectious fevers. On the other hand, should severe vitamin A deficiency exist, it seems likely that the local epithelial changes occurring in mucous membranes would provide a favourable condition for the entrance of infections of various sorts, and, by analogy with vitamin A deficiency in animals, one would expect infections, largely by local organisms, to occur in children with vitamin A deficiency. However, there seems at present no way of establishing that, for example, pneumonia recorded as having occurred in a vitamin A deficient child was due to the vitamin A deficiency rather than, let us say, to a deficiency of vitamin D and C or of iron. There is one type of infection which is frequently recorded on vitamin A deficient diets on which Hess[41] lays stress, namely infestation with intestinal parasites.

Xerophthalmia associated with disease of the liver.—Blegvad[5] draws attention to the occasional occurrence of keratomalacia in persons who are suffering from hepatic disease, and suggests that this is due to poor fat absorption in such cases. In the light of evidence now existing to show that the liver is the main storehouse of vitamin A in the body, it is probable that both deficient absorption and deficient storage of the vitamin has occurred in such cases, and this suggests the need for paying particular attention to the vitamin A intake in persons with disease of the liver. Wright[111] stresses the association of keratomalacia with liver disease in India, where infantile biliary cirrhosis is relatively common.

Skin lesions associated with idiopathic steatorrhoea (**Gee's disease**).—The so-called coeliac disease of children, or idiopathic steatorrhoea of adults, is a disease with nutritional disturbances associated with defective absorption of various foodstuffs, important among which is fat. These patients are extremely liable to symptoms of deficiency of one of the fat soluble vitamins, vitamin D, and can be cured of the symptoms of rickets and tetany by increasing the vitamin D available to the body. Are they also liable to symptoms of vitamin A deficiency? Parsons[77a], in a masterly account of coeliac disease in a recent text book, states that with this disease xerophthalmia 'is rarely seen, although an instance is reported by Schick.' Bennett, Hunter and Vaughan[3a], in their account of 15 cases of steatorrhoea in adults and adolescents, say that 'the frequent occurrence of skin lesions in the present series appears too striking to be mere coincidence. They were noted in seven cases and described by the dermatologists as psoriasis, eczematous or pustular dermatitis.' They suggest that deficiency of the vitamin B complex may be responsible for the skin lesions in some cases, but it is certainly tempting to suppose that some of the skin lesions were associated with vitamin A deficiency, more especially as at least one of their cases suffered from loss of hair. What part, if any, vitamin A deficiency may play in other symptoms of coeliac disease, for example the abdominal distension, attacks of diarrhoea, stunted growth and occasional apparent voracious appetite, it is impossible to say. It is probable that many of these symptoms are of mixed origin as the nutritional deficiences are multiple, but vitamin A deficiency may well be one factor.

Mortality.—The mortality with xerophthalmia and keratomalacia shows wide variations; as one might expect, it is highest in infants and diminishes during childhood. In Blegvad's series, the majority of whom were infants with keratomalacia, that is were very young and also suffering from fairly advanced disease, he estimated the mortality to be 21·5 per cent.: of those under 3 months old 39 per cent died, and of those over 12 months old only 11 per cent. Bloch[8], in Denmark, studying cases of a similar type thought that probably one-third of the cases died before they reached 8 years of age, and that the mortality was highest in babies under 6 months old. On the other hand, Mori[74], although unable to give figures for the mortality, since his cases were out-patients, thought that among those adequately treated few died. His cases, however, were older, mostly between 2 and 5 years old, and in the great majority the eye changes were at an earlier stage than in Blevgad's series. Nevertheless, Mori stated that in Japan thousands of children died yearly from the diarrhoea (which at that time he attributed to insufficient animal fat) or recovered blinded from xerophthalmia. Stephenson[95] says that to his knowledge nearly half his babies with keratomalacia (average age 4½ months) died, but most of his cases did not receive the dietetic treatment now known to be necessary. On the other hand, most of the school children he examined with xerosis he considered in tolerably good general health[94]: hence presumably the mortality among them was small.

The commonest cause of death varies in different localities: diarrhoea would appear to be the most common, but pneumonia, as already shown, is mentioned by many writers.

Post-mortem findings in the human subject.—As in the rat, guinea pig, and monkey, so in the human subject dying from vitamin A deficiency, characteristic epithelial changes are found. One of the fullest descriptions of post-mortem findings is that of Wilson and Du Bois[105], who made a post-mortem examination on a 5 months old baby dying with keratomalacia.

> The infant was emaciated, the skin was dry and felt waxy, and the corneae were cloudy. The characteristic epithelial changes already described were present in the trachea, bronchi, lungs, renal pelvis, uterus, pancreatic ducts, submaxillary ducts and other parts, and these changes were associated with local inflamations. There were inflammatory changes in the lachrymal and salivary glands (the latter an extremely common site of abscess in the rat); cyst-like cavities with fibrosis and inflammation in the pancreas, and emphysema and bronchiectactic cavities with abscess formation in the lungs. Thus the pathological changes found in the human subject closely corresponded with those found in experimental animals.

The eye signs also arise from changes in the character of the epithelium. The epithelium of the conjunctiva may become a stratified epithelium many rows deep. Kreiker[51] says that in the first stage of xerosis the goblet cells of the conjunctiva disappear and gradually the conjunctival epithelium loses its normal character and becomes more like epidermis. Later, the superficial layers of epithelial cells undergo hyaline degeneration, and below these ‘ cornification ’ occurs. The appearance of Bitôt’s spots is due to the casting off of stratified epithelial cells, the hyaline degeneration giving the ‘ oily ’ appearance mentioned by some writers. The changes which occur in the cornea are of the same type.

Response to treatment with vitamin A.—As already shown, the use of liver or liver oil in night blindness and keratomalacia is both ancient and widespread. Nearly sixty years ago Snell[91] was systematically using cod-liver oil for the eye disease in this country. Some clinical writers, as for example, M. Mori[74], came as near fixing upon the curative agent as was possible before the existence of fat soluble vitamins was recognized. Mori knew deficiency of animal fats brought about the disease, and that certain oils, for example, cod-liver oil, were potent therapeutic agents. Once vitamin A was postulated from animal work and its association with eye changes in the rat was established, the eye lesions in the rat were quickly recognized as corresponding with the eye changes carefully described in the human subject so many years before.

As a result of the animal investigations, however, the means of cure has been put upon a scientific basis, and for this reason is already much more systematically used for the human disease.

It is generally agreed that unless the disease is very advanced, treatment with vitamin A causes steady improvement. The eye symptoms respond well, and night blindness, occurring without objective eye changes, may be cured in as short a time as 12 hours[1] up to 2 to 3 days: a single large dose of cod-liver oil will abolish this symptom at least temporarily. Spence[92] found that Bitôt’s spots were diminished within a week of beginning regular treatment with cod-liver oil, and disappeared in the worst cases by the fifth to sixth week. Xerosis disappeared in another 10 to 15 days, and in his cases all signs disappeared within 2 months. Mori[74] states that in Japan, where there is a well-marked seasonal incidence, the slighter cases improve without active treatment in the late autumn and in winter, but may relapse again the following year. Xerophthalmia has been cured in breast-fed infants by giving the mother cod-liver oil (Shiele, quoted by Blegvad[5]), though it would seem unwise in such a serious disease to trust to this indirect method of medication.

Under treatment with cod-liver oil, the skin rapidly becomes moister; pyrexia disappears; skin lesions heal or disappear; the abdomen, if enlarged, becomes smaller; diarrhoea probably clears up; and if there has been an excess of epithelial cells in the urine, these disappear. Weight usually improves, and there is a steady improvement in activity and health.

Studies of the effect of vitamin A administration either prophylactically or in acute infections.

So far we have considered the disease 'vitamin A deficiency' as revealed in the records of persons suffering from night blindness, xerophthalmia or keratomalacia, and have suggested that these eye changes are far from being the earliest changes in the disease. It is, therefore, interesting to consider what light has been thrown by other types of investigation on the symptomatology of vitamin A deficiency in man.

Of late years much attention has been focussed on the possible part played by vitamin A deficiency in increasing susceptibility to infection, and it has been suggested that reduced immunity due to vitamin A deficiency is widespread or that vitamin A is a special 'anti-infective agent.' An attempt is, therefore, made below to give a very brief survey of the subject from this aspect. No increased immunity to infections has been demonstrated as the result of giving an excess of vitamin A to persons already getting an adequate supply either in a good general diet or in the form of a cod-liver oil supplement.

Thus Wright, Frosst, Puchel and Lawrence[109] in the Montreal Foundling and Baby Hospital, found no reduction in the common upper respiratory infections in a group of babies given vitamin A concentrate in addition to the cod-liver oil which was given to all infants as a routine measure. Again, lads in a Royal Air Force technical school, getting a good diet, who were given a large daily dose of vitamin A, suffered from a roughly similar incidence of minor respiratory infections to those noted in the controls (actually the vitamin A group showed a very slight advantage, but the difference was not statistically significant[65]).

Vitamin A as a purely prophylactic agent has also been studied in groups of persons who, it was thought, might have received an inadequate supply of the vitamin in their diet.

For example Barenberg and Lewis[3] compared the incidence of respiratory infections in babies receiving partly skimmed milk (a diet which one would suppose might well be deficient in vitamin A), with other groups of babies in the same institution getting either extra vitamin D or extra vitamin A and D combined, and found no significant difference between the groups. The groups, however, were fairly small.

The interpretation of the work of Green, Pindar, Davis and Mellanby[34], in connection with puerperal infection, is complicated by the simultaneous administration of vitamins A and D. They gave extra vitamins A and D combined to a large group of pregnant women and reported a greatly reduced incidence of puerperal pyrexia in women so treated as compared with controls. On the other hand, Burton and Balmain[10] carried out Dick tests on pregnant women and on patients convalescent from scarlet fever, both groups being treated with vitamins A and D combined, and also carried out Dick tests on controls, but failed to reveal any influence of these vitamins on the result of the Dick reaction.

Hence none of these observations can be regarded as establishing the existence of any widespread vitamin A deficiency, nor the value of vitamin A as a prophylactic agent against general infections, since all positive results may be ascribed to the action of either vitamin A or vitamin D or both, or else numbers are too small to establish any conclusions. The prophylactic administration of vitamin A to babies described in Part II suggests that among infants slight vitamin A deficiency is not uncommon and that extra vitamin A diminishes the incidence of skin infections. In other words, susceptibility to skin infections is probably the first sign of vitamin A deficiency in infants. If this be so, then more information concerning the prevalence of vitamin A deficiency should be obtainable by using this vitamin in the treatment of skin infections.

To some extent this has already been attempted. Thus Kuipers[52], van Gulik[103] and Prakken[83] have each treated the eczema seborrhoicum of infants with vitamin A, with or without an acid in addition. The two first writers claim benefit from this treatment, but Prakken failed to confirm their results. The present author is now engaged at the Queen's Hospital for Children on work concerning the value of vitamin A in the treatment of skin infections.

Vitamin A has been given as a therapeutic agent during the course of acute infections, for example, in puerperal septicaemia, pneumonia, measles and scarlet fever. Unfortunately in most of these observations vitamins A and D have been given together, which makes it impossible when beneficial results have been claimed to assess the part played by either separately.

The extensive observations of Orenstein[76] and his colleagues on pneumonia in South Africa are not open to this objection. Their investigations appear to have been thoroughly controlled, and are clear cut. They used a vitamin A concentrate alone, without added vitamin D, for the treatment of native mine workers with pneumonia, because it had been suggested that the diet of these workers was deficient in vitamin A. However, it was proved that extra vitamin A did not affect the mortality rate, length of stay in hospital, or the complications and sequelae in their patients. Donaldson and Tasker[20] had previously carried out observations, on a smaller scale, on pneumonia cases and considered their results favourable, but they had apparently employed beef liver and a combination of vitamins A and D, so that a clear interpretation of their results is not possible. In 1929 Mellanby and Green[69] suggested, as a result of a small series of observations on cases of puerperal septicaemia, that vitamin A was of value in the treatment of this condition. However, their observations also were complicated by the simultaneous administration of vitamins A and D, and, as far as the author is aware, the value of vitamin A in such cases has not yet been confirmed.

Another disease on which some interesting work has been done is measles. Ellison[22] treated 300 cases with vitamins A and D combined, and compared them with 300 control cases. Control and treated cases appear to have been well matched, and whereas the death rate in the control group was 8·7 per cent. that in the treated group was only 3·7 per cent. These figures seem to indicate that the vitamin treatment was of considerable value, but they leave unsettled the question whether vitamin A or vitamin D, or both, were material factors. Since the maximum seasonal incidence of both measles and rickets is in the late winter and early spring months, it seems likely that many of these patients from poor homes may have suffered from vitamin D deficiency, in which case the results described might be entirely due to the extra vitamin D given. A curious point is that although the mortality rate was less than half in the vitamin treated group, yet the incidence of otitis media was just about the same in the two groups. Sutliff, Place and Segool[96] carried out similar observations on cases of scarlet fever, their object being to compare the incidence of otitis media in cases given extra vitamins A and D and in those not so treated. They arrived at the conclusion that the vitamin supplements were ineffective in reducing the incidence of otitis.

If vitamin A deficiency is playing an important part in increasing susceptibility to severe infections which may cause death, then careful post-mortem examination, with particular attention to the presence or absence of the epithelial changes characteristic of vitamin A deficiency should go a long way towards settling the question. Certainly existing knowledge would seem to indicate that infections occurring in vitamin A deficient animals are the direct result of pathological changes in the epithelium. Hence if at a human post-mortem examination these changes are definitely absent, then one might legitimately assume that the infection was not the result of vitamin A deficiency. It is, however, obvious that very extensive examination would be necessary to establish such a negative result.

Studies of the vitamin A content of the human liver and blood.

Four different workers: Wolff[107] in Holland, both Moore[73] and Green[35a] in England, and Fox[27] in South Africa, have approached the question of vitamin A deficiency from another standpoint. They have estimated colorimetrically the vitamin A value of the livers of persons dying from different causes, hoping in this way to find some correlation between the cause of death in different groups of cases and the amount of vitamin A in the liver. The figures obtained varied enormously. In persons dying of accidents, and supposed to be otherwise healthy, the values obtained varied from 0 to 1,210 blue units per gramme of liver (Wolff[107]). Even in a supposedly homogenous group of adult males, all on the same ration, and all dying as the result of accident, Fox found the blue value varying from 12 to 938. The values obtained by Fox for persons dying of accident (12 to 938) and for those dying from pneumonia (0 to 483) who had also been on the ration, showed a wide overlap, though the pneumonia cases showed a lower average value. In the present state of our knowledge, it seems likely that if the same series had been estimated biologically (an impossibly large undertaking), the two methods would have often given discrepant results. Nevertheless, certain considerations of great interest emerge from these studies. They strongly suggest that persons with liver disease, or degeneration of liver cells, have a deficient storage capacity for the vitamin[35a]. Other features of interest are that persons dying of organic heart disease, bronchitis, kidney disease and septicaemia, as well as new-born infants, give low average values; on the other hand, diabetics, presumably on account of the nature of the diet prescribed, have high average values. At present it is impossible from these observations to draw any general conclusions as to whether or not widespread vitamin A deficiency exists in the countries where the work has been done, or to assess the part played by vitamin A deficiency in lowering resistance to infection.

Clausen[13] in a preliminary report on 'carotinemia and resistence to infections,' concludes, from a statistical analysis of the diets and respiratory infections of 700 children under 3 years old, that vitamin A deficiency may account for some severe infections. He found that carotine is present in the blood at birth, and rises by 2 years old to an average of 0·075–0·100 mgm. per 100 c.c. in the plasma. The average values for healthy children were low in the winter months, namely, December to February.

Summary.

This paper attempts to construct from the literature on the subject a clinical account of the disease 'vitamin A deficiency,' with special reference to children.

Incidence.—The disease is stated to be common in India, China, and the Far East, as well as in some parts of Central America and Labrador. In Europe it is probably much less common now than it was during the last century; in this country cases of sufficient severity to give rise to keratomalacia, or even to xerosis of the conjunctiva, are apparently comparatively rare. Since, however, in many cases eye changes are clearly not the earliest symptoms, it is possible that the disease is present in many areas where it has passed unrecognized. Whether or no vitamin A deficiency of slight grade is frequent in this country is a debatable point: the evidence submitted in Part II suggests that it is common in infants. Persons of any age may be affected, but children are more susceptible than adults, and the younger the child the greater the susceptibility. The deficiency is most likely to occur in the poorest sections of the population. There exists no satisfactory evidence to show that vitamin A deficiency is a common cause of any of the usual respiratory or intestinal infections occurring in children in this country.

Diets deficient in vitamin A.—The eye symptoms produced by vitamin A deficiency have usually occurred on high carbohydrate diets, or sometimes on a diet of skimmed milk. The dietaries have usually contained little or no eggs, meat, animal fat, or green vegetables, and have consequently been deficient in more factors than one. No quantitative knowledge exists as to the vitamin A requirements of children. A breast-milk diet may, under some circumstances, provide insufficient vitamin A for a baby.

The clinical picture of vitamin A deficiency.—If we imagine a case of established vitamin A deficiency in a child, we would probably picture a child of very poor parents, thin, undersized and apathetic and suffering from a variety of dietetic defects and very probably also from complicating infections. If the patient is a baby, he will probably be marasmic and have keratomalacia; if a school child, he may be well grown or undersized and eye symptoms are likely to be less severe. Severe vitamin A deficiency rarely, if ever, occurs alone. If we nevertheless try to imagine a child suffering from the effects of vitamin A deficiency alone, the following seems the probable clinical course (the order of onset of the different symptoms varying from case to case):—

A child, otherwise apparently in good health, develops an increased susceptibility to infections of the skin; he may have boils, sores, impetigo, or napkin rash or other evidence of skin sepsis, and this susceptibility continues throughout the disease, the lesions often being chronic. In the next stage, the texture of the skin itself undergoes a change and becomes dryer than normal, and may show desquamation. The dryness will probably not affect the skin of the face. A papular or 'acne-form' eruption may be present on extensor surfaces. There are usually periods of looseness of the bowels, sometimes a chronic diarrhoea sets in, occasionally constipation appears, and the rate of growth is retarded. The child loses the alertness of health and may be very lethargic. The hair loses its normal gloss, and if the child belongs to a dark skinned or yellow race, some slaty pigmentation of the conjunctiva and skin will probably appear. The voice may become hoarse and there may be bronchitis. The child may show great eagerness for food, and a large abdomen. By this time, if the patient is old enough and he is watched when playing in the dusk, evidence of night blindness will probably be present; it is apparently invariably present before there is xerosis of the conjunctiva. The first objective eye change in a white skinned child may be either conjunctivitis, or dryness of the conjunctiva with the formation of Bitôt's foam spots; and by the time these have appeared the weight will probably be stationary. There is often irregular pyrexia, which is more likely to be noted in hot climates as it probably results from diminished sweating and consequent diminished heat loss. If the case is still untreated and the deficiency severe, the child will grow thinner, subcutaneous fat is lost, the skin becomes shrivelled, there is powdery and flaky desquamation of the skin, the hair falls out and the eye changes progress with involvement of the cornea. In an advanced case there is marked wasting, with shrivelled, dry, desquamating skin, large numbers of epithelial cells in the urine, pyrexia, loss of appetite, extreme apathy; and corneal changes which frequently produce blindness, together with infections of both skin and eye. If there has been exposure to strong sunlight there may be some bleaching of the hair. Death occurs most often from diarrhoea or from pneumonia. In an older child the disease runs a slower course, in a young infant a much more rapid course, and the younger the child the worse the prognosis. The order of appearance of symptoms varies: in some cases one group of symptoms, and in other cases another will predominate, but by the time objective eye changes are present it is probable that evidence of change in other epithelial tissues will also be present, for in most cases it seems that they precede the eye changes.

Mortality.—The mortality for established cases of vitamin A deficiency varies greatly. With adequate treatment, even in advanced cases, it is probably small, unless the child is acutely ill with an infection. Without specific vitamin A treatment the mortality among babies is very large; among older children much smaller.

Post-mortem changes.—The characteristic post-mortem changes are in the epithelium and occur simultaneously at many sites; cuboidal or columnar epithelium is transformed into epithelium of a squamous type, and squamous epithelium becomes keratinized. Infections apparently gain entrance as a direct result of this epithelial change.

Treatment.—If treated early with adequate doses of vitamin A, for example in the form of cod-liver oil, the prognosis at all ages is good; and without other treatment, eye changes, skin changes, hoarseness, diarrhoea, voracious appetite and pyrexia all diminish and disappear. If treatment is begun late, though life may be saved, vision will probably be lost.

Conclusion.

It is hoped that this attempt to summarize our clinical knowledge of vitamin A deficiency may lead to the collection of more evidence regarding its incidence. If the syndrome described is borne in mind, it is hoped that clinicians may recognize the disease at an earlier stage, and in some cases at least establish its identity by the therapeutic test of giving vitamin A without other forms of medication. If pathologists will keep the condition in mind, and examine for the characteristic epithelial changes, evidence should be forthcoming as to whether or not vitamin A deficiency is a common cause of infections bringing about death. Apart from these fatal infections, evidence is required as to whether or not vitamin A deficiency is an important factor predisposing to skin infections, and on this subject further investigations are in progress. It is possible that the much higher incidence of skin infections in the lower social strata than in the higher, is more a matter of diet than of soap and water.

Up to now no satisfactory evidence is available proving the value of vitamin A administration (without other therapeutic measures) either in the prophylaxis or the cure of any of the common acute infections present in this country.

The possibility that vitamin A deficiency plays a part in certain common diseases of the central nervous system has been suggested, but clinical work bearing on this problem is not at present available.

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THE SOLAR IRRADIATION OF CHILDREN WITH SPECIAL REFERENCE TO HYPERVITAMINOSIS D.

BY

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Various aspects of solar irradiation have been studied and many important discoveries have been made during the past few years. Probably the most significant was that made by Huldschinsky when he discovered the beneficial effect which followed exposure in infantile rickets. His work was quickly followed up by other workers and the subject investigated in considerable detail. Not only natural sunlight, but artificial sunlight was used during these investigations.

In 1921, Powers, Park, Shipley, McCollum and Simmonds[1] showed that by irradiating with a mercury quartz vapour lamp rats which had been fed on a rickets producing diet, the occurrence of rickets could be prevented. Hess and Unger[2] exposed rachitic children to natural sunlight, and found that the condition improved as evidenced by a deposition of lime salts at the wrist epiphyses. That the effect was general and not local was demonstrated by the fact that increased calcification occurred at both wrists although only one arm had been irradiated. Hess, Pappenheimer and Weinstock[3] showed that the beneficial effect was due to the ultra-violet rays and was lost when plain glass was interposed. In the same paper they showed that protection ,against rickets is effected by rays of a wave-length of 313 μμ or less. Hess and Gutman[4] showed that after exposure of rachitic children to natural sunlight the blood inorganic phosphorus, previously low, as is usual in rickets, increased to normal figures, the rickets subsiding at the same time. Kramer, Casparis and Howland[5], using a mercury quartz vapour lamp raised the blood phosphorus of rachitic children from 2·7 to 6·0 milligrammes per 100 c.c. blood. Hess and Gutman[4] noted that these results are comparable to those obtained by the administration of cod-liver oil in rickets.

For some time it was difficult to understand the mode of action of sunlight in its effect on rickets, and why the results should be similar to those obtained with cod-liver oil. Vitamin D was known to be the substance in cod-liver oil which cured rickets. But why should vitamin D result from irradiation of the skin? It was found that the exposure of lipoid-containing foods to ultra-violet rays caused them to assume anti-rachitic properties. A sterol was suspected as being the vehicle for the vitamin D and the evidence pointed towards cholesterol. This stage of the investigation has been summarised by Pfannensteil[6]: Hess succeeded in irradiating cholesterol. Rosenheim, and Pohl, showed by spectral absorption tests that cholesterol was not the pro-vitamin, but found that absorption bands in the spectrum pointed to ergosterol. Irradiation of this substance proved it to be the substance which provided the vitamin D.

Ergosterol is present as an impurity in cholesterol. It can normally be obtained from fungi, principally ergot, and from yeast. The cod probably gets it from the plankton of marine algae in which it is said to be present. This accounts for the presence of vitamin D in cod-liver oil. Hess and Lewis[7] mention the beneficial effect in rickets which followed the administration of irradiated ergosterol. Hess[8] and Hess and Weinstock[9] showed that pieces of irradiated skin from infants and calves were anti-rachitic when eaten by rats. Hume, Lucas and Smith[10] showed that vitamin D could be absorbed through the skin.

The chain of evidence appears to be complete. The beneficial effect of ultra-violet rays in rickets is due to the activation in the skin of ergosterol and the liberation and absorption of vitamin D.

Another aspect now presents itself in considering the effect of prolonged solar irradiation. Is it possible to activate vitamin D in injurious quantities? It is manifestly impossible to assay the quantities being liberated and absorbed except by their remote effects.

During experimental work with irradiated ergosterol it was found that the doses necessary to procure protection against and to cure rickets were minute. Rosenheim and Webster[11] found that 1/10,000 mgm. daily cured rickets in rats, and prevented the occurrence of rickets in rats fed on a rachitogenic diet. They suggest that the smallest protective dose is probably about 1/50,000 mgm. daily. This dosage is agreed upon by many workers on the subject. Harris and Moore[12] draw attention to the very small dosage and suggest the need for determining whether or not an injurious overdosage is likely to occur readily. They point out that in the cases of fat soluble vitamins instances of hypervitaminosis have been recorded. They found in experiments that young rats lost weight rapidly and died when receiving a synthetic diet containing 0·1 per cent. irradiated ergosterol. This is equivalent to 100,000 times the minimal protective dose. The animals suffered from anorexia, diarrhoea, inanition and bad condition of coat prior to death. These results occurred only when activated ergosterol was given and did not follow when the ergosterol was non-irradiated or had been inactivated by over-irradiation. Pfannensteil[6] states that overdosage of vitamin D led to death of rabbits, and that Kreitmar and Moll verified this. According to Rosenheim and Webster[11] a dose of 10,000 times the minimal effective dose produced no ill effects in rats.

Harris and Moore[13] suggest that there are two threshold values for vitamin D, a minimum and a maximum. Below the minimum altered calcium and phosphorus metabolism results with deficient calcification. Above the maximum threshold signs of toxicity occur.

The question of the specificity of vitamin D in producing toxicity and the possibility that the toxicity might vary with the means of extraction has been raised. Dixon and Hoyle[35] using irradiated ergosterol extracted in oil failed to produce toxicity. Harris and Moore[13] have investigated this point and show that toxicity can be produced using both alcoholic and oily extracts of vitamin D. They realise that it is impossible to deny the existence of hypothetical toxic by-products, but suggest that the characteristic calcium-phosphorus disturbance points to the vitamin. They suggest that possibly Dixon and Hoyle gave doses which fell short of the threshold necessary to produce toxicity.

The signs of toxicity have been described by many workers, and there is general agreement that there is anorexia, loss of weight, diarrhoea and cachexia. In addition to these Harris and Moore[13] include a rise in blood phosphorus, and urine saturated with calcium salts.

These writers record the post-mortem findings: emaciation, atrophy of the spleen and thymus, calculi in the bladder, and deposits of calcium salts in the kidneys, heart-muscle, pyloric end of the stomach, aorta and colon. Microscopic examination revealed extensive deposition of calcium salts in the tunica media of the aorta, in the medulla, cortex and pelvis of the kidneys, and in the duodenum and small intestine. Hypercalcaemia and the deposition of calcium salts has been found to have occurred by all workers who produced signs of toxicity with irradiated ergosterol (Harris and Stewart[11]; Pfannensteil[6]; Smith and Elvove[15]; Policard, Paupert-Revault and Barral[16]; Taylor, Weld, Brannion and Kay[17]; Ashford[18]; Levaditi and Li Yuan Po[19]; Klein[20]).

The symptoms and signs of toxicity all point to a gross disturbance of the calcium-phosphorus metabolism, but the huge doses apparently necessary in rats and rabbits would indicate that a large margin of safety exists. Taylor, Weld, Brannion and Kay[17], however, show that in dogs this margin of safety is not so high, and suggest that human tolerance is about the same.

It has already been pointed out that the calcium-phosphorus metabolism in rickets is stimulated by the administration of a limited amount of sunlight. The administration of an unlimited quantity of sunlight may cause excessive stimulation. This is one of the points to be decided in this paper.

Present investigation.

In making these observations two series of children were used. With three exceptions they were between the ages of six and fifteen years. All were patients receiving treatment for various orthopaedic conditions at the Country Branch of the Royal National Orthopaedic Hospital. The conditions for which they were receiving treatment are stated in Table 1.

TABLE 1.

CLASSIFICATION OF DISEASES.

SERIES I.	No. of Patients.
Tuberculous disease of spine	4
,, ,, hip-joint	6
,, ,, knee-joint	2
,, ,, ankle	1
Deformities of spine—non-tuberculous	2
Diseases of hip-joints ,, ,,	5
Osteomyelitis of metatarsal bone	1
Epiphysitis ,, ,,	1
Poliomyelitis—deformity	1
Spastic paraplegia	1
Peroneal muscular atrophy	1
Infective arthritis in knee-joint	2
Bone abscess—tuberculous	1
SERIES II.	
Tuberculous disease of spine	6
,, ,, hip-joint	6
,, ,, knee-joint	2
,, ,, ankle-joint	1
,, ,, shoulder	1
,, abscess of tibia	1
Rickets—old-standing, healed	1
Anterior poliomyelitis	1
Malunited fracture	1

In Series I the children were new admissions, the majority being from congested districts in which they would not have obtained much pure sunshine.

A preliminary clinical examination was made on admission and specimens of blood, urine and faeces were collected. The children were then exposed to sunlight. These examinations were repeated at intervals of three or four weeks during the period of observation. The examinations were divided into two groups, clinical and biochemical. An enquiry was made into previous clinical history, with special regard to any condition which might cause abnormal findings. Cases in which there was a possibility of previously damaged renal function were rejected.

The clinical examination consisted of an investigation of the various systems. The condition for which the patient was admitted to the hospital was noted as such and was not described in detail. Special mention was made of the reaction to the sun as shown by the degree of pigmentation attained. The weight was noted and the blood pressure taken with a mercury manometer. The systolic pressure was taken as the measurement of the mercury in the tube at the moment of reappearance of the pulse sounds in the brachial artery at the elbow after the artery had been obliterated by a higher pressure. The diastolic pressure was taken as being the measurement at which soft sounds followed the appearance of short, sharp knocks. Bearing in mind the possibility of calcification of the arteries, a special clinical note was made as to the condition of the radial artery at the wrist as far as could be determined by digital pressure. Examination of the abdomen consisted only of palpation, special attention being given to the kidney areas in an effort to elicit tenderness such as might be caused by renal stone. No renal x-rays were made.

The technique for collection of specimens for biochemical examination was as follows :—

BLOOD. Twenty c.c. of blood were withdrawn from the median cephalic or basilic vein into a Record syringe. The analyses carried out on blood were estimations of non-protein nitrogen, urea, calcium, inorganic phosphates, cholesterol, haemoglobin, total solids, and alkali reserve.

URINE. A twenty-four hour specimen was collected, usually from 8 a.m. to 8 a.m. The analyses consisted of the volume output in 24 hours, specific gravity, reaction, estimation of urea and examination of the centrifuged deposit. All specimens were also examined for abnormal constituents such as sugar, albumen, blood and acetone bodies.

FAECES. No aperient was given for at least forty-eight hours before the specimen was obtained. Specimens of faeces were examined for the presence of occult blood by the benzidine and guiacum test. A microscopical examination was also carried out. A complete analysis on the fat content was done which included estimating total and neutral fat and the free fatty acid content.

After the first clinical examination and collection of the first specimens the children were exposed to natural sunlight. In the majority of cases, exposure was given while the children were recumbent. A few were up and about. The length of the exposure was limited during the early stages in order to prevent too severe a skin reaction, but once an immunity had been established, as much natural sunlight as was available was administered. The hours of sunshine recorded at Greenwich during the period of observation are given in Table 2. The entire body surface was exposed where possible. In many cases only one aspect could be insolated. The degree of reaction to the early doses, and the degree of pigmentation obtained, were noted. For purposes of comparison the degrees of pigmentation are divided into : erythema, light brown, golden brown and dark brown. No artificial sunlight was used.

TABLE 2.

HOURS OF SUNSHINE RECORDED AT GREENWICH.

April to October, 1930.

April	107·0
May	136·4
June	227·4
July	157·7
August	227·2
September	119·4
October	104·5

Diet.—The diet received was the customary full hospital diet with a sufficiency of all essentials, well balanced, with possibly a slightly greater amount of fat than is usual. Plenty of fluids were administered, mostly in the form of water. Extra quantities were given on hot days when the children were exposed to sunlight.

The period during which these observations were carried out was from May to October.

Series II consisted of twenty cases who had had insolation either before admission or during previous summers. Similar examinations to those stated above were made in this series at the end of the summer, and were not repeated.

Commentary.

The results of clinical observations in Series I are not given in tabulated form in view of space requirements. The number of examinations recorded is greater in the earlier than in the later cases. The reason for this is that there was no object in continuing the observations later than October, and the number of new admissions was not sufficiently large to enable all the cases to be examined over a similar period of time. The earliest cases were those admitted in May. Observations were not made on any cases admitted after July.

The degree of pigmentation attained a maximum at about the period from the end of June to the middle of July. This can be attributed to two reasons, (1) the greater amount of sunlight during the preceding two or three weeks, and (2) the greater inclination of the sun, giving a larger number of ultra-violet rays. After this period the degree of pigmentation diminished in intensity.

The general condition improved steadily in all cases, the most marked improvement being that noted soon after admission. In no case was any marked loss of appetite noted even during the periods giving the greatest hours of sunshine. In all but one an increase in weight occurred and the general condition showed improvement. With regard to the local condition, in most cases an improvement was shown, but in three cases it was no better.

The heart was normal in every case except one. In this child a doubtful aortic diastolic murmur was thought to have been present at the fourth examination, but the heart sounds had previously been normal.

The blood-pressure readings fell within normal limits. In some cases they were on the low side. In fifteen cases the pressures at the end of the observation period were higher than those noted at the beginning; in eleven cases the reverse occurred. Intermediate readings did not show any progressive change.

Digital examination of the radial artery at the wrist failed to show any definite change except in one case where a note was made that the artery 'feels harder than before.'

Examination of the abdomen revealed no abnormality, either on admission or during the period of observation.

BLOOD. The non-protein nitrogen, urea and cholesterol fell for the most part within normal limits, and any marked variation which occurred in one or two of these constituents were unconfirmed by abnormal readings in the remaining one or two. Thus, the cholesterol was as high as 260 mgms. per 100 c.c. blood in two cases without there being any indication of pathological change. In twenty-two cases the blood cholesterol was higher at the end of the experiment than at the beginning, and this rise was in most cases progressive. Haemoglobin and total solids showed results which are normal or lower than normal. There was apparently no tendency towards dehydration. The alkali reserve showed a general tendency to fall slightly in twenty-one cases, against a rise in six. Here, again, the figures are normal.

The blood calcium and phosphorus figures are those which show definite and progressive changes. In the majority of cases the serum calcium showed a tendency to rise during the period of observation. This occurred in seventeen patients as against a fall in six. Although most of the terminal readings may be taken as higher than is usual they do not lie outside normal limits. It is interesting to note that the highest serum calcium levels do not necessarily follow the sunniest periods.

The blood inorganic phosphorus shows an increase during the period of observation in all but two cases. In the main the increase is a gradual one, but a few cases show a drop in the second or third readings followed by a rise. The majority of cases shows that the increase continues up to the end of the period, and that the terminal values are the highest.

URINE. The quantity of urine passed in twenty-four hours was a little below normal in most instances, and definitely low in a few. It was sufficiently high, however, to show that there had been no gross dehydration and that the quantity of fluids taken had been adequate. The specific gravity fell within normal limits and bears out the observation that there had been no undue concentration. The reaction of the urine was usually acid. Occasionally a neutral or alkaline urine was noted without any apparent significance.

The urinary urea figures were definitely low in the greater number of cases. There does not appear to have been any progressive failure of excretion of urea during the period of observation. When taken in conjunction with the blood urea the combined observations show that there can be no suggestion of diminished renal function. Again, the low figures have less significance in view of the fact that no attempt has been made to measure the nitrogenous intake.

In seven cases a trace of sugar was found in one or two of the specimens which have been examined. These are apparently instances of alimentary glycosuria.

Rothera's and Gerhardt's tests show the absence of any ketosis.

A large number of cases showed albuminuria. In twenty-three cases albumen was present, though always in small amounts. Its appearance varied, sometimes being present in the first or second, but more often in the later specimens. Albumen was constantly present in only one case. In ten cases the patients were boys and in thirteen girls.

In six cases a trace of blood was detected in the urine. In two of these pus was also present.

The deposit showed pus cells in five cases, red blood corpuscles in three, epithelial cells in nine. The crystalline deposit was usually calcium oxalate, the next most frequent being phosphates, with a few uric acids and urates.

FAECES. In the greater number of cases the total amount of fat excreted was about normal, and the results of the fat digestion are within normal limits. In a few instances in which the total amount of fat excreted was high the increase was usually most marked in the neutral fat.

Microscopic examination revealed the presence of starch granules or striped muscle fibres in one or more specimens from all but six cases. The sparcity of these substances and the normal, or almost normal fat metabolism deprives them of any significance.

Discussion.

The literature which has been read in connection with the subject under review deals mostly with the effect of insolation on the calcium-phosphorus metabolism, and in particular with the effect of insolation in infantile rickets. Within our knowledge a complete report of the effects of exposure to sunlight such as has been made in this paper has not been previously recorded.

The general sense of comfort and lazy well-being which results from solar irradiation, and the pleasant effect of lying exposed to a warm sun are well known and much sought after by those to whom they are available.

Rollier[21] in his book 'Heliotherapy' gives a detailed review of the historical and biological aspects of solar insolation, and stresses the necessity for control of the quantity administered. He also mentions the individual response and susceptibility to exposure as shown by general reactions and by the degree of pigmentation attained. The ultra-violet ray value of the sun, and probably also the actual heat of the sun to which his patients were exposed are considerably in excess of those which are obtained in the district in which the present observations were made. As a result one might expect that individual and general reactions would not be so marked in the present cases. This was found to be the case within certain limits. Some of the patients developed an earlier and a more severe erythema than others, and the degree of pigmentation attained showed individual variations to the same amount of sunlight. The degree of pigmentation has been regarded by Rollier as of prognostic value in his treatment of tuberculous patients, those pigmenting most being likely to respond to treatment more readily than those in whom the pigmentation is less marked. In this connection it cannot be said that any difference in healing was noted in the tuberculous patients with differing degrees of pigmentation in this series. Apart from the reaction as evidenced by degree of pigmentation no general reactions were found to occur. The patients seemed to enjoy insolation and did not suffer from undue drowsiness or from loss of appetite.

The response of the calcium-phosphorus metabolism to sunlight through the medium of vitamin D has already been briefly referred to in the opening section of this paper in relation to its effect on rickets (Kramer, Casparis and Howland[5]). In rickets, however, one is dealing with patients in whom there is a pathological depletion of calcium and phosphorus and the result of treatment is to restore to the blood the normal quantities of these substances.

Can the normal amounts of blood calcium and phosphorus be increased by the action of sunlight, and if so can this increase amount to injurious proportions? Other factors than the quantity of sunlight administered must be taken into account, the most important being the balance of the mineral intake in the diet. This is referred to by Orr as a necessity for the maintenance of general health. Henderson[22] in his experiments on the effect of ultra-violet irradiation on calcium and phosphorus retention in pigs stresses this point, and notes that on a well-adjusted diet the influence of light is at a minimum. The importance of the subject is also referred to by Harris[23] in his work on hypervitaminosis D with irradiated ergosterol. Hart, Steenbock and Elvehjem[24] found that the blood phosphorus showed a marked and persistent increase when goats with a negative calcium balance was irradiated daily for twenty minutes.

Granted a normal diet, however, what variations in the blood calcium and phosphorus levels can occur apart from the action of vitamin D? Havard and Reay[25] showed that variations in the levels of blood phosphorus occur during the course of the day. Differences up to 14 per cent. occurred between the first and second estimations made in a man who had just walked a short distance in the morning. A definite rise up to 16 per cent. above morning levels occurred at times in midday specimens. During sleep a rise of 20—50 per cent. was noted with a rapid fall on awakening.

As a result of the action of sunlight the same observers note a rise in blood phosphorus figures between January and August. The values were lowest in the first month, an average of 2·9 mgm. per 100 c.c. blood, which rose to 4 mgm. in August. Hess and Lundagen[26] showed the occurrence of a seasonal rise in the blood phosphorus in infants. Sixty infants between the ages of six months and eighteen months, fed on an adequate diet, were used. The blood phosphorus was found to be lowest in March, average about 3·85 mgms. per 100 c.c. blood and highest in June, when the readings averaged 4·22 mgms. The phosphorus intake was fairly rich in these cases. The children were not exposed to the sun to any marked extent, normal clothing being worn. In a series of ten older children the change was less marked. In adults, members of the medical staff, no change was noted. Hess[8] showed that not only phosphorus but calcium was raised in the blood by ultra-violet rays. The calcium was more stable. He mentions the seasonal incidence of tetany. The blood phosphorus rise as a result of irradiation is also reported by Grant and Gates[32]. Havard and Hoyle[34], however, failed to produce a rise in the blood calcium and phosphorus winter levels by irradiating two adults for sixteen days with a mercury quartz vapour lamp. The substances are evidently more stable in adults than in children. (Hess and Lundagen[26].) In one case of the present series this point is further illustrated. This was a youth aged 19 years. The blood phosphorus figures showed no increase during the period of insolation.

From the above it can be seen that the normal calcium-phosphorus metabolism is affected by sunlight. In the observations made above, however, the amount of irradiation was limited either by the length of exposure or by the extent of body surface insolated. With unlimited exposure to the sunlight in this country and the greater extent of body surface exposed, would the calcium-phosphorus metabolism be still further affected, and if so in sufficient amount to constitute hypervitaminosis D?

Hypervitaminosis D.—In dealing with this subject recourse must be had to the work done in connection with the action of large doses of irradiated ergosterol. That the mode of action of sunlight and of irradiated ergosterol is through the same mechanism has been shown earlier in this paper. It is reasonable to assume, therefore, that the signs and symptoms of overdosage will be similar.

Basing their estimates on the results of animal experiments most observers consider that the doses necessary to cause injurious effects would be so large as to render the possibility of overdosage impracticable. Thus Light, Miller and Frey[27] from their experience gained by experiments on rats suggest that for infants a harmful dose of irradiated ergosterol would be 1·5 litres per diem of a solution with a potency one hundred times as great as that of cod-liver oil. Hess, Lewis and Rivkin[28] think that the importance of these investigations has been over-rated.

The degree of the susceptibility of various animals to vitamin D has been studied by Taylor, Weld, Brannion and Kay[17]. They found that the degree of resistance diminishes in mice, chickens, rabbits, cats, dogs successively. In the case of dogs the susceptibility is marked and an instance is given in which death followed the administration of irradiated ergosterol when the amount given had a potency only twenty times the maximal therapeutic dose for an infant. They found that puppies were more susceptible than adult dogs. The symptoms of toxicity were general depression and lethargy, weakness, diarrhoea and vomiting. Hypercalcaemia was present. Hess and Lewis[7] describe two cases of toxicity in infants receiving five milligrammes of irradiated ergosterol daily. The symptoms in dogs and infants are strangely similar. Both are typical of overdose of vitamin D and were caused by amounts not much in excess of therapeutic doses. Levaditi and Li Yuan Po[19], however, found that monkeys appeared to be less susceptible to overdosage than other animals.

The amount of ergosterol which can be stored and irradiated in the skin is not known. Nor is the rate or extent of its absorption from the skin capable of accurate measurement. It has been previously mentioned that Hume, Lucas and Smith[10] were able to prove absorption of vitamin D through the skin in rabbits by painting on a small depilated area, inaccessible to the mouths of the animals, a solution of irradiated cholesterol, and so preventing the onset of rickets although the diet given was a rickets-producing one. Evidently the power of absorption from the skin is fairly high.

Taylor, Weld, Brannion and Kay[17] have studied the effects of administration of irradiated ergosterol by various routes. The conclusions they arrive at are that when given intravenously the therapeutic effect and toxicity are the same as when given orally. When injected subcutaneously, however, the vitamin was found to be less effective in producing hypercalcaemia or other signs of overdosage. In comparative tests on six puppies, using oral, intramuscular and subcutaneous routes, two puppies for each method, and giving those in which the oral administration was used only half the dose of the other two, it was found that the 'oral' pups showed symptoms in forty-eight hours, and died in five to eight days. The 'subcutaneous' pups lived for twelve and eight days, and were bright after a week, while the 'intramuscular' group took a middle course. In the animals receiving the vitamin by the subcutaneous and intramuscular routes an initial depression of serum calcium was found to have occurred. The writers suggest that the comparative ineffectiveness of irradiated ergosterol when given subcutaneously may be of physiological importance. It may be that over-irradiation of the body surface will result in storage of vitamin D and that some mechanism exists whereby quantities of the vitamin excessive to the body's needs are rendered inert. Also they suggest the probability that the pigment found in the skin is a protective mechanism designed to prevent excessive activation of ergosterol. Hess[8], and Hess, Pappenheim and Weinstock[9] have found that black rats require more irradiation to be protected against rickets than do white rats. In support of their hypothesis that there is some mechanism regulating the quantity of irradiated ergosterol absorbed, Taylor, Weld, Brannion and Kay[17] suggest that pigmentation alone could not protect against the absorption of ergosterol secreted and irradiated on the surface of the skin or in the layers of the epidermis superficial to the pigment layer.

The above factors would tend to suggest that the activation and absorption of excessive amounts of vitamin D by irradiation of the body surface is unlikely to occur.

Before discussing the results of the observations and examinations made in this series of cases, it would be well to set out the signs and symptoms of hypervitaminosis D. In the cases of animals these have already been mentioned and the pathological findings outlined. Cases have been reported in children, however, three of which will be detailed here.

Hess and Lewis[7] report two cases occurring in infants. One infant, after five milligrammes of irradiated ergosterol daily, developed moderate fever, vomiting, drowsiness, and loss of weight. The serum calcium was 16·2 mgm. per 100 c.c. blood. The blood phosphorus was about normal. The other case was similar and the condition resembled dehydration. In one of these patients hypercalcaemia recurred after three weeks further dosage, a month having elapsed since the previous trouble. Here the serum-calcium rose to 14·7 mgm. per 100 c.c. blood. Gain in weight continued till the twenty-fifth day when the serum calcium rose to 17·6 mgm. per 100 c.c. blood. Then vomiting and loss of weight occurred. The coagulation time of the blood was shortened. Electric muscular reactions were sluggish. A trace of albumen and granular casts were present in the urine.

A fatal case of hypervitaminosis D is reported by Thatcher[29] which is worth describing in detail.

In this case the patient was a boy aged eighteen months, weighing 15½ lb., and in length 29 inches. The child was pale, puny, and thin. There was no evidence of rickets. Albuminuria was present and the infant developed pyuria and acetonuria. The mentality was dull; vomiting occurred. The blood urea was

90 mgm. per 100 c.c. blood. The systolic blood pressure 78 mm. of mercury The urine was acid and contained pus, red blood corpuscles and granular casts. The condition was diagnosed as a case of pyelo-nephritis. Death ensued and at post-mortem examination the kidneys were large, firm, pale yellow, with tiny grittish particles in medulla, especially at bases of pyramids. Microscopically, deposits of calcium were found in the medulla and in the lumen of the collecting tubules. Fibrous tissue had formed about some of the calcium deposits. There were no calcium deposits in other organs. The spleen was healthy, the thymus small and the liver showed some fatty degeneration. The bones were well calcified, though some demineralization was present. The comment made was that the changes resembled hypervitaminosis D. Subsequent investigation revealed the fact that ʒiv of irradiated ergosterol emulsion had been given daily from May to September. This amounted to twice the curative dose. The diet which this patient had been receiving was half to three quarters of a pint of cow's milk daily, some thin farinaceous food, orange-juice and a proprietary meat-juice.

Thatcher suggests that the demineralization may have been due to deficient diet, but it may have been due to excess of blood phosphorus, apt to occur in babies a few weeks after administration of vitamin D has begun. In this case the serum calcium and phosphorus have not been recorded although the deposition of calcium in the renal tissues suggests that hypercalcaemia was present. The two cases reported by Hess and Lewis showed definite hypercalcaemia and in one the blood phosphorus was ' about normal.'

It has been seen that the predominant feature of hypervitaminosis D is a severe disturbance in the calcium-phosphorus metabolism, most marked in the case of calcium. Hypercalcaemia and the laying down of calcium salts form a constant feature. It is interesting to note the mechanism through which this occurs. Although the subject has been controversial it seems to be fairly well established that vitamin D acts on the calcium-phosphorus metabolism through the medium of the parathyroid glands. The signs and symptoms of parathyroid overdosage have been found to agree accurately with those caused by overdosage with irradiated ergosterol. (Taylor, Weld, Brannion and Kay[17]; Collip and Clarke[30]; Jones, Rapoport and Hodes[31].) Smith and Elvove[15] point out the possibility of calcium precipitation through lowered carbon dioxide tension. Calcium deposition is most likely to occur in the lungs, kidney and aorta.

In the cases under review symptoms and signs which could be attributed to hypervitaminosis D have not occurred. The general health of the patients remained good throughout the period of observation. Mentally they were bright and cheerful. No instance of undue drowsiness was observed. No case of anorexia can be recalled. There was no diarrhoea. The state of nutrition was good. No vomiting occurred which could not be readily accounted for.

Serum calcium. The slight increase in serum calcium which has been noted in many cases is within normal limits, and bears out the observation made by Hess[8]. In one case the serum calcium rose as high as 12·5 mgm. per 100 c.c. blood, but no symptoms were observed. In the remainder of the cases the calcium figures were between 9 and 12 mgm. per 100 c.c. blood.

BLOOD PHOSPHORUS. The definite and progressive increase in the inorganic blood phosphorus which has occurred during the period of insolation also corroborates the findings already recorded (Havard and Reay[25]; Hess[8]; Hess and Gutman[4]; Grant and Gates[32]). The figures are actually higher than those mentioned by these workers. Few of the initial estimations are lower than 4 mgm. per 100 c.c. of blood, and many rise to levels above 6 mgm. A mild hyperphosphataemia has occurred as a result of the insolation. There is no apparent reason for the drop in the blood phosphorus which was seen in two cases.

Other constituents of the blood in this series of cases show normal figures.

HAEMOGLOBIN. The haemoglobin value of the blood was found by Hess, Poncher, Klein and Dale[33] to be lower in twelve infants receiving maximum doses of irradiated ergosterol than in those receiving lesser doses. Jones, Rapoport and Hodes[32] found the hæmoglobin value was normal in dogs receiving large doses.

NON-PROTEIN NITROGEN. Collip and Clarke[30] noted a terminal rise in non-protein nitrogen in dogs receiving large doses of parathyroid extract.

CARBON-DIOXIDE TENSION. Smith and Elvove[15] suggest that lowered carbon-dioxide tension might cause precipitation of calcium salts.

URINE. The occurrence of albuminuria in such a large number of cases is difficult to explain. In six instances it was associated with the presence of pus cells, evidently the result of a mild pyelitis or cystitis, or due to tuberculous infection of the kidney. On five occasions red blood cells were present, with or without pus cells. Tuberculous infection is the more likely in the latter cases. The presence of epithelial cells does not call for any special interpretation. The absence of casts excludes an interstitial nephritis such as has been described by some investigators of hypervitaminosis D as being present in that condition (Smith and Elvove[15]).

FAECES. Apart from the remarks already made no interpretations can be made as a result of the examinations.

Series II.—Observations made on the cases in this series, and the results of the biochemical examinations do not differ from those in Series I. Exposure during successive summers evidently does not produce cumulative effects.

Conclusions.

As a result of the exposure of the present series of children suffering from various orthopaedic conditions to all the available sunlight between the months of May and August, 1930, it has been found that no clinical ill-effects occurred. In no case can it be said that the progress of the patient was retarded as a result of the insolation. The marked improvement in the general condition which followed admission might be attributed partly to a beneficial effect resulting from exposure to the sun.

Although the amount of insolation obtained was not the maximum possible it was sufficient to demonstrate that there is little or no likelihood of producing ill-èffects due to excessive liberation of vitamin D which had been produced by irradiation of the ergosterol contained in the skin. The increase in the serum calcium and phosphorus which was found to have occurred was within physiological limits. No signs of toxicity such as have been reported by investigators of hypervitaminosis D have been demonstrated.

Taking the combined calcium-phosphrous metabolism into consideration it appears that on a normal diet doses of vitamin D such as are produced by irradiation cause a greater increase in the blood phosphorus than in serum calcium.

Summary.

1. A series of twenty-eight children has been exposed to solar irradiation during the summer months. Clinical examinations and biochemical investigations have been made periodically during the period of observation. A further series of twenty children has had similar tests made at the end of the summer.

2. No ill-effects have been observed as a result of the insolation.

3. An increase in the blood calcium and phosphorus values has been demonstrated during insolation.

4. No evidence of excess production of vitamin D has occurred.

It is a pleasure to record our thanks to members of the Staff of the Royal National Orthopaedic Hospital, who have kindly allowed us to investigate their patients.

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PYELONEPHRITIS IN INFANCY AND CHILDHOOD: ITS BACTERIOLOGY AND PATHOLOGY*

BY

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Until about twenty-five years ago it was generally accepted that pyelitis was a disease per se and that infection of the renal tissue proper was as a rule secondary to infection of the pelvis. Recently, however, it has been shown that the lesion is seldom localized in the pelvis and a considerable amount of evidence has accumulated which favours the supposition that the primary focus of infection is in the kidney itself (Thiemich[1], Borrmann-Bremen[2], Kowitz[3], Chown[4], Wilson and Schloss[5]).

In the present investigation the bacteriological findings in 87 cases of pyuria are recorded. In 25 of these the formation of agglutinins was studied and in 9 complement-fixation tests were carried out. The lesions found at 170 post-mortem examinations are described and in 70 of these the kidneys were examined histologically.

It was found that 78·2 per cent. of the 170 cases occurred in the first year of life. As only fatal cases are dealt with, this figure does not give the true age incidence of pyuria, but it suggests that it is more fatal in infants than in older children. Girls were found to be more frequently affected than boys, in the proportion of 2 to 1, but in children under six months there was little difference in the sex incidence. This finding is in agreement with the observations of others (Kowitz[3] Chown[4], Wilson and Schloss[5], Spence[6]).

TABLE 1.

Age and sex incidence of fatal cases of pyuria.

Age groups.	Cases		Percentage of total cases.
	Boys.	Girls.	
Up to 26 weeks	33	43	44·7
26 weeks to 1 year	12	45	33·5
1 to 13 years	10	27	21·8
Total	55	115	
Percentage	32·4	67·6	

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Bacteriology.

Cultures were obtained from the urine of 87 cases of pyuria. The greatest care was always taken to avoid contamination of the specimens in the process of collection. The organism was first cultured on MacConkey's medium and on nutrient agar and from the colonies grown subcultures were made in various sugar media and the resulting reactions noted. When streptococci were found their resistance to heat and haemolytic properties were investigated. The organisms of the coli group were further identified by their agglutination reactions to antisera. Some difficulty was experienced in the preparation of the antisera as sometimes the animals rapidly failed after the commencement of the inoculations. This was overcome by injecting 0·5 c.c. collosol manganese intramuscularly at the same time as the animal was inoculated with the organisms. Further, it was noted that living organisms were tolerated better by the animals than killed ones.

From the urine of 87 cases 9 different types of organisms were obtained, the bacteria most commonly present being the various coliform bacilli. In some of the specimens of urine more than one organism was obtained. Table 2 shows the order of frequency of the occurrence of the different types. From the table it will be noted that coliform bacilli were the organisms most commonly identified and that of these b. coli communis and b. MacConkey 71 occurred most frequently. The fact that these are two of the commonest inhabitants of the bowel (MacConkey[7] and Mackie[8]) favours the view that lesions of the urinary system are often due to auto-infection from the bowel.

TABLE 2.

TYPES OF ORGANISMS FOUND IN 87 CASES OF PYURIA.

87 cases	Pure coliform 51	21	B. coli communis.
		17	B. MacConkey 71.
		3	B. paracolon.
		3	B. proteus.
		3	Non-lactose fermenters.
		2	B. paracolon. B. MacConkey 71.
		1	B. paracolon. B. lactis aerogenes.
		1	B. paracolon. B. acidi lactici.
	Pure streptococcal 11	11	Enterococcus.
	Pure staphylococcal 2	2	Staphylococcus aureus.
	Mixed 23 Enterococci together with	7	B. coli communis.
		7	B. MacConkey 71.
		5	B. proteus.
		2	B. paracolon.
		1	B. lactis aerogenes.
		1	Non-lactose fermenter.

When the agglutinating properties of the organisms were studied it was found that organisms having identical cultural properties did not correspond serologically. The antisera prepared to b. coli communis, b. MacConkey 71 and b. paracolon agglutinated the homologous organisms in dilution of 1 in 3,200, 1 in 6,400 and 1 in 12,800 respectively. When, however, the antiserum to b. MacConkey 71 was tested against 12 other strains of culturally identical bacilli recovered from the urine of other patients agglutination only occurred in high concentrations of the serum, e.g. 1 in 40. Coliform bacilli giving different sugar reactions, etc., from these obtained with the various strains of b. MacConkey 71 were not agglutinated at all. Similar findings were obtained with 13 strains of b. coli communis and 4 strains of b. paracolon isolated from the urine of pyuria cases when tested against the appropriate antisera. Thus, while antisera are of use in identifying individual members of the coliform group, they are, on account of their strict specificity, of limited value for the differentiation of groups of organisms giving the same sugar reactions. This is in accordance with the work of Mackie[8] and suggests that only autogenous vaccines are likely to be of any benefit in treatment.

Agglutination tests with patients' sera.—In 25 cases of pyuria agglutination tests were carried out with the patients' sera against the organisms isolated from their urine. When agglutination in dilution of 1 in 40 or over was obtained the results were considered to be positive. Thirteen of the 25 cases (52 per cent.) showed positive results, the titre varying from 1 in 40 to 1 in 3,200. Six of these, all under 1 year, died, while there was only one fatal case in the 12 where the serum did not show agglutinins (Table 3). The kidneys of 4 of the patients who died, in whom the sera agglutinated, were examined histologically and abscesses found. Similar lesions were also found in the single fatal instance among those where the sera did not agglutinate.

TABLE 3.

RESULTS OF AGGLUTINATION TESTS WITH PATIENTS' OWN SERA.

INFECTING ORGANISM.	AGGLUTINATION WITH PATIENT'S SERA.			
	Positive.		Negative.	
	Recovered.	Died.	Recovered.	Died.
B. coli communis	6	2	4	1
B. MacConkey 71	1	2	2	0
B. paracolon	0	2	2	0
B. proteus	0	0	2	0
B. lactis aerogenes	0	0	1	0
Total	7	6	11	1

In two of the fatal cases the infecting organism was b. coli communis and the agglutination titre was 1 in 80 and 1 in 40 respectively; in two other children the organism isolated was b. paracolon and the titre of the patients' sera was 1 in 2,560 and 1 in 160 respectively. In the remaining two subjects who died, b. MacConkey 71 was present in the urine and the titre of the patients' sera was 1 in 640 and 1 in 160 respectively. In the 7 children who did not die and who gave positive agglutination tests, 6 girls and 1 boy, 3 were under one year and 4 were aged 3, 4, 7 and 8 respectively. Six of these children were acutely ill for several weeks with high fever and then gradually recovered. The seventh child was not acutely ill and the agglutination results were somewhat anomalous, for agglutination was obtained with normal serum in the same dilution as that obtained in the patients' serum. In these 7 cases b. coli communis was present in 6 and in the seventh b. MacConkey 71. The titre of the sera of the patients infected with b. coli communis was 1 in 3,200, 1 in 400, 1 in 320, 1 in 160, 1 in 80 and 1 in 40 and that of the child infected with b. MacConkey 71 was 1 in 40.

Case report.—The patient in whom the highest titre (1 in 3,200) was obtained showed certain points of interest and the following are the chief details:—

The patient was a girl aged 34 weeks. She had been healthy until one week before admission when diarrhoea began. On admission to hospital the child was drowsy, feverish and appeared acutely ill. Both kidneys were palpable, especially the left. The urine contained abundant pus cells and b. coli communis. A fortnight after the onset of the illness an agglutination test was performed when it was found that with a 1 in 3,200 dilution of the patient's serum the infecting coliform bacilli were completely agglutinated. Six weeks later when the child's condition had improved slightly, the test was repeated, but the agglutination titre of the patient's serum had fallen to 1 in 400. An autogenous vaccine was then prepared and given to the patient at weekly intervals. Three days after the first dose the titre was 1 in 160 and a month later, 1 in 80. The child was dismissed well one month later and the urine was free from pus and organisms, while the kidneys were no longer palpable.

This case is of interest because agglutination was at its height when the child was acutely ill and as her condition improved the agglutination titre declined.

Of the 12 cases which showed no agglutination 7 were in children under one year. Of these, 2 (one boy and one girl) showed little constitutional disturbance, while 4 girls were acutely ill with high fever, but the condition cleared up rapidly under treatment with sodium bicarbonate. The seventh case, a boy of 25 weeks, died nine days after the onset of the disease. The blood serum was tested for agglutinins on the fourth day of the illness with negative result. It is to be regretted that the agglutination test was not repeated at a later date as it is probable that when the test was made agglutinins had not had time to make their appearance. There were 5 cases over one year, all females, and in 4 of these frequency and pain on micturition were prominent symptoms. The fifth patient, aged 3 years, was acutely ill on admission with high fever. They all made good recoveries under treatment with sodium bicarbonate.

From the results of the agglutination tests it would appear that neither the type of infecting organism nor the sex or age of the patient seems to affect the agglutination results. The production of agglutinins appears to depend on the general resistance of the patient and on the severity and extent of the lesions. In support of the latter view it was found that all but one of the fatal cases showed positive agglutination tests whereas other children who were acutely ill on admission, but who recovered quickly, gave negative results.

Complement fixation tests.—In 9 of the 25 cases in which agglutination tests were performed, the sera were also examined for antibodies by complement-fixation tests. Each serum was tested in 8 tubes containing complement varying in amount from 2 to 40 minimal haemolytic doses. One of the early cases showed zonal fixation of complement when doses up to 40 minimal haemolytic doses were added to the antigen-antiserum mixture: accordingly, throughout the experiments both untreated complement and complement treated with charcoal were used to remove the natural immune-bodies to certain organisms of the coli-typhoid group present in guinea-pig's serum (Dunlop[9]). From Table 4 it will be seen that 4 of the 9 sera tested gave positive complement fixation results and 3 of them also agglutinated the infecting organism. On the other hand, of the 5 sera in which the complement-fixation test was negative 2 gave negative and 3 positive agglutination tests. It would appear that the results of the tests do not run strictly parallel with the agglutination findings, nor does the production of complement-fixing antibodies seem to depend on the type of infecting organism. Further, it was found that neither the age, the sex, the general condition of the patient nor the extent of the lesion appeared to influence the results.

TABLE 4.

COMPARISON OF COMPLEMENT-FIXATION AND AGGLUTINATION TESTS.

Organism.	Complement-fixation.	Agglutination.	No. of cases.
B. coli communis	+	+	2
	–	+	2
	–	–	1
	+	–	1
B. MacConkey 71	+	+	1
	–	+	1
	–	–	1

Pathology.

At post-mortem examination definite inflammatory lesions were noted in the kidney substance in 84 of the 170 cases investigated, and of these the pelvis was congested in 58 and the bladder in 39. In the remaining 86 cases there were varying degrees of congestion and cloudy swelling in the kidneys, with congestion of the pelvis in 66 and of the bladder in 32. As the post-mortem findings in patients dying of pyogenic infection of the urinary tract probably only show the most advanced stages of the inflammatory process, it was thought that earlier changes might be found in patients dying of some other disease but who had pus in their urine. Sixteen cases of this nature were studied. In all of these the kidneys showed congestion or cloudy swelling, with congestion of the pelvis in 9 and of the bladder in 8.

Histology.—Of the cases coming to autopsy portions of the kidneys, pelves, ureters and bladder of 70 were examined histologically, and were divided into four groups according to the severity of the microscopic lesions present. In the first group there were 18 children, in 16 of whom pyuria, often of only a few days' duration, arose during the course of some other illness and was not directly the cause of death. In the remaining two cases the pyuria was primary. In all of these little change was noted in the kidneys, apart from congestion of some of the glomeruli and cloudy swelling in the epithelial cells of the convoluted tubules. The pelves in 14 showed varying degrees of acute inflammatory reaction, and similar changes were noted in the bladder in 7. These minor lesions in the kidneys, such as congestion of the glomeruli and cloudy swelling in the tubules, may represent the earliest stage of the reaction to the infection. In 14 of the cases coliform bacilli were cultured from the urine and in one this organism was actually seen in sections of the glomeruli. Although the infection of the urinary tract in these cases was mostly of a secondary nature, it is unlikely that the reactive changes to the infection would be different from those met with in primary cases and they probably represent the earliest phase of the inflammatory process.

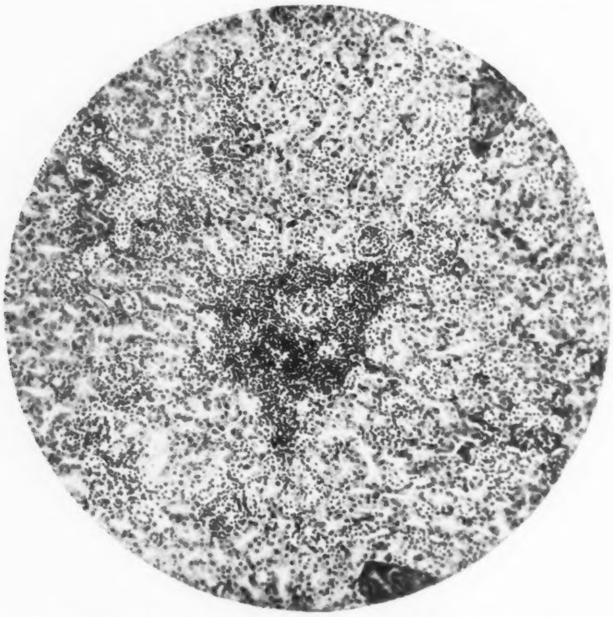

FIG. 1.—Section of kidney from case of pyelonephritis. (Female, aged 7 months.) In the cortex a small perivascular area of round-celled infiltration is present. Haematoxylin and eosin. × 60.

The second group was composed of 4 cases in which more marked histological changes were found in the kidney substance than in the first group. Small foci of dense, round-celled infiltration (Fig. 1) were present in the interstitial tissue as well as the slight changes, e.g., congestion of the glomeruli and cloudy swelling in the epithelial cells of the tubules, which were noted in the first group. The pelvis was congested in all 4 cases, but the bladder in only one. In all of the cases coliform bacilli were isolated from the urine. The cases in the second group were considered to have died at a more advanced stage of the disease than those in the first group.

The third group, in which there were 16 cases, showed definite acute inflammatory lesions in the kidney substance and other parts of the urinary tract. In the kidney there were widely separated foci of polymorphonuclear infiltration of the interstitial tissue and frequently these formed actual abscesses. In these areas, which were often wedge-shaped with the base of the wedge towards the surface of the kidney, the tubules were distended with polymorphonuclear leucocytes and desquamated epithelial cells. The glomeruli showed varying degrees of congestion. These inflammatory foci were situated chiefly in the cortical regions. The pelvis in only 3 of these 16 cases showed definite inflammatory change, and in one of these a similar lesion was noted in the bladder. In the other two cases, in addition to the lesions in the kidneys, foci of inflammation were found in the bladder microscopically, but not in the pelvis. In 15 of these cases coliform bacilli were isolated either from the urine during life or from the kidney abscesses post mortem. In the sixteenth staphylococcus aureus was grown from the abscesses in the kidney.

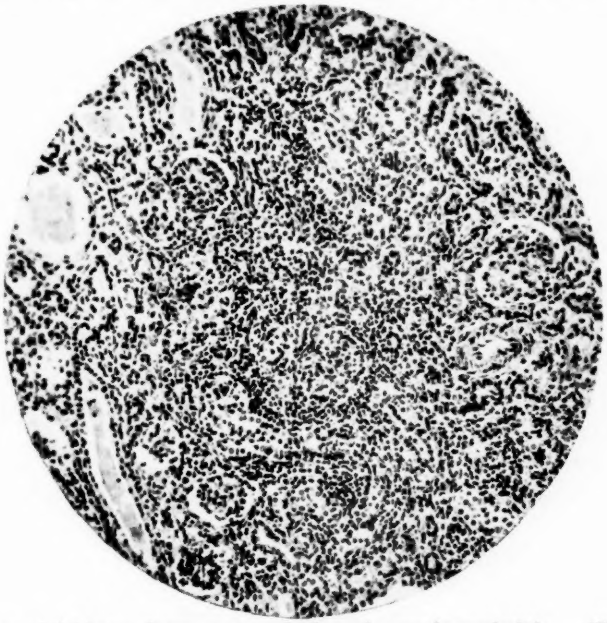

FIG. 2.—Section of kidney from case of chronic pyelonephritis. (Female, aged 4½ months.) In the cortex there is an area of round-celled infiltration in the interstitial tissue. Haematoxylin and eosin. × 90.

The 32 cases comprising the fourth group showed a less acute course and more chronic lesions than in any of the foregoing groups. These lesions consisted of widely separated foci of round-celled infiltration of the interstitial tissue (Fig. 2) and, in some cases, areas of early fibrosis. Some of the tubules in these areas contained polymorphonuclear leucocytes and desquamated epithelial cells, and the glomeruli showed only minor degrees of congestion. The lesions were often wedge-shaped with their bases along the surface of the cortex, causing small irregular, vascular, depressed areas on the surface of the kidney (Fig. 3, 3a, and 4). Such areas corresponded roughly in shape and distribution to the areas of polymorphonuclear infiltration noted in the acute cases. Scattered through the kidney substance

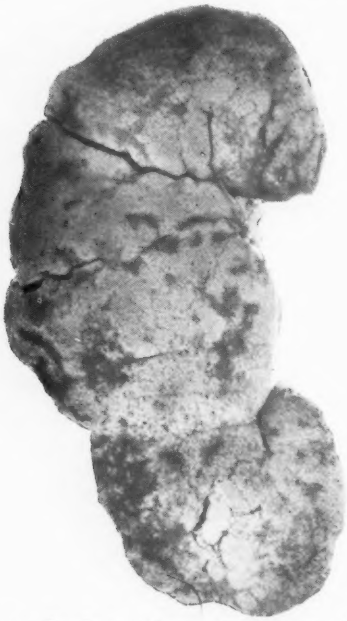

FIG. 3.—Surface view of kidney from case of chronic pyelonephritis. Numerous irregular small vascular depressed areas are present. The larger depressions are due to foetal lobulation. Natural size (Museum of Royal Hospital for Sick Children Glasgow).

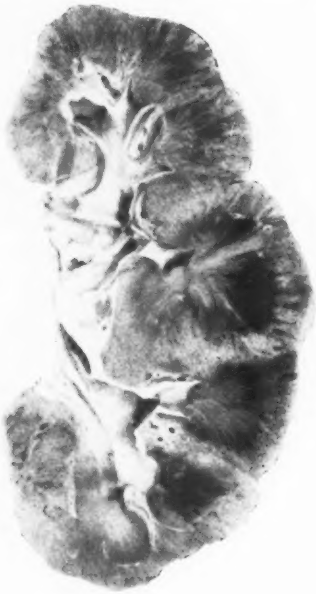

FIG. 3A.—View of cut surface of chronic pyelonephritis. (Same kidney as Fig. 3.) Many small irregular depressed wedge-shaped areas are present in the cortex. Natural size (Museum of Royal Hospital for Sick Children, Glasgow).

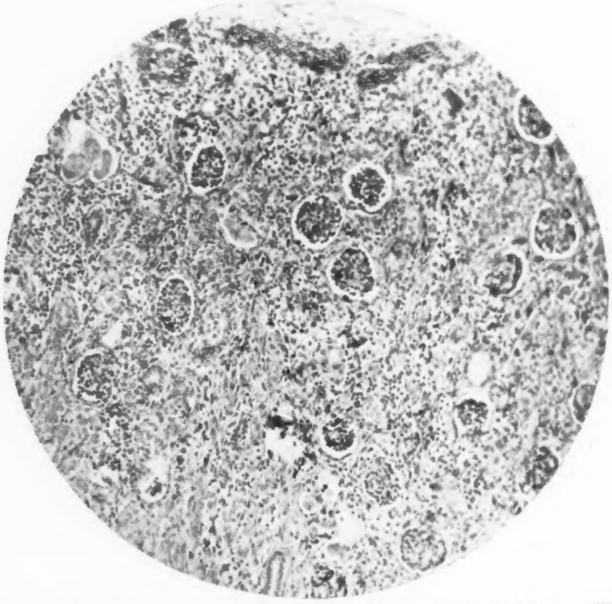

FIG. 4.—Section of kidney from case of chronic pyelonephritis. (Female, aged 5½ months.) The cortex shows a depressed vascular area on the surface. There is slight round-celled infiltration of the interstitial tissue immediately under the capsule and some early fibrosis. Haemotoxylin and eosin. × 67.

in some of these cases were foci of polymorphonuclears but these probably represented a recrudescence of infection. In only 8 of these were there inflammatory lesions in other parts of the urinary tract. The pelves were affected in 4, the bladder in 2 and in the remaining 2 both the pelves and bladder were affected. In 30 of the cases coliform bacilli were found in the urine and streptococci in 8. In one staphylococcus aureus was found.

From the morbid anatomical and histological findings it is evident that in the fatal cases of pyuria in infancy and childhood the kidney substance is often the seat of an inflammatory change more marked than that found in the pelvis. Indeed, the pelvis frequently shows no lesion either on naked eye or on histological examination. In 70 cases in which the kidneys were shown histologically to be affected the pelvis showed inflammatory lesions in 27 and the bladder in 15. The common lesion in such cases is therefore suppurative nephritis rather than simple pyelitis. This is in agreement with the findings of many other workers. Death occurs in many cases when the lesion is in the acute stage, yet in some there is evidence of an attempt at healing as shown by areas of fibrosis, while in others death may occur when the condition has become subacute as shown by the presence of scattered patches of round-celled infiltration. It is possible that, in cases where the infection is overcome, the only permanent damage may be widely separated foci of fibrosis in contradistinction to the diffuse fibrosis of chronic interstitial nephritis.

Pathway of infection.—A study of the present series of cases brings out some points in favour of the descending route of infection. The fact that in infants under six months of age, a time of life when the vulva is specially exposed to infection, the proportion of males affected is almost equal to that of females is evidence that in young children at any rate the route of infection is not up the urinary passages. This point has been commented on by other workers[3, 4, 5]. In older children, however, females are more commonly affected than males and it is possible that in some of these infection spreads from below. It is known that primary pneumococcal peritonitis is more common in females than in males (McCartney and Fraser[10]) and it is probable that in this disease the organisms frequently gains access to the peritoneum via the genital passages; similarly in the underclad children of the poorer classes renal infection may spread upwards from the vulva.

In 70 cases of the present series in which histological examination of the kidney, renal pelvis and bladder was made only 35 showed lesions outside the kidney and of the 48 cases with gross renal damage only 13 showed pelvic or bladder lesions. It seems improbable that if the infection spreads upwards inflammatory reaction in the lower urinary passages should be so relatively infrequent, for one would have to assume either that the inflammatory changes in the pelvis and bladder had healed, leaving no trace, or that infection could reach the kidneys without producing changes in the intervening tissue; both of these explanations seem improbable. Lastly, the histological appearance of the lesions is in favour of a haematogenous spread. In the early cases the glomeruli and convoluted tubules showed the most notable changes while in the more advanced cases the cortex of the kidney was as a rule more seriously damaged than the tissue adjacent to the pelvis. If infection had spread from below it is probable that the tissues furthest removed from the pelvis would be least affected.

Conclusions.

1. The post-mortem findings of 170 cases of pyuria in infants and children are recorded. In 70 of these the kidneys were examined histologically. In 87 cases the bacteriological results are recorded. In 25 of these the formation of agglutinins was studied and in 9 complement-fixation tests were carried out.
2. Coliform bacilli were the organisms most commonly isolated suggesting that pyuria is due to auto-infection from the bowel.
3. Great specificity to agglutination was shown by the coliform organisms. For this reason only autogenous vaccines are likely to be of benefit.
4. Agglutination of the organisms isolated from the urine with the patient's serum occurred much more commonly in the fatal cases than in those that recovered. Acutely ill patients whose serum did not agglutinate recovered quickly. Probably the development of agglutinins depends on the extent and severity of the lesions in the kidneys and on the general resistance of the patient.
5. The power of fixing complement did not run strictly parallel to the agglutinating properties of the serum.
6. The morbid anatomical and histological findings indicate that the lesion is a suppurative nephritis affecting especially the renal cortex and that these lesions may either heal leaving scar tissue or become subacute and show scattered foci of round-celled infiltration.
7. The cortical distribution of the lesions and the relatively infrequent infection of the pelvis and bladder point to a blood infection in most cases.

I wish to record my gratitude to the members of the clinical staff of the Royal Hospital for Sick Children, Glasgow, for permission to consult their case reports, and also to Professor G. B. Fleming for his interest in this work. I also have much pleasure in acknowledging the valuable advice and criticism of Dr. J. W. S. Blacklock, of the Department of Pathology of the University and Royal Hospital for Sick Children, Glasgow. Some of the photographs are by Mr. John Kirkpatrick, of the Department of Pathology, Glasgow University.

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A NUTRITIONAL DISEASE OF CHILDHOOD ASSOCIATED WITH A MAIZE DIET—AND PELLAGRA

BY

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In a recent issue of the 'Archives of Disease in Childhood,'[1] under the first part of the title given above, Dr. Cecily D. Williams gave a very interesting account of a syndrome found among the native children between one and four years old in the Gold Coast Colony, which she states has not been described before. The syndrome consists 'of oedema, chiefly of the hands and feet, followed by wasting, diarrhoea, irritability, sores, chiefly of the mucous membranes, and desquamation of areas of skin in a manner and distribution which is constant and unique,' and results, it is believed, from an improper diet containing an excess of white maize.

Dr. Williams categorically denies that this affection is pellagrous and has given her reasons. These appear to be based on standard text-book descriptions of the disease which, unhappily not always very comprehensive or correct, have misled her into using fallacious criteria for differential diagnosis. Without having seen these cases in Accra, I am venturing to dispute the correctness of the diagnosis and to suggest that they are cases of pellagra.

The history of these infant patients is that they begin to get irritable, the skin and hair lose their normal colour and glossiness, there are attacks of diarrhoea, slight oedema of the hands, feet and face but the skin is not dry and there is 'no branny desquamation as in pellagra.' Suddenly, at the end of seven to ten days black patches appear on the skin of the extensor surfaces about the ankles, knees, wrists and elbows which spread so that 'soon the legs and forearms, knees and elbows are covered with a sort of crazy pavement of this thickened epidermis.' These thickened crumpled and darkened patches then exfoliate leaving a pink raw surface exposed underneath. 'The patches of desquamation progress up the thigh and may become severe on the buttocks. Very small patches may also be seen on the face, back and elsewhere.' It may be noted that the blackened patches on the skin appear first where there is any focus of irritation or pressure.' In spite of having given a really very excellent description of a pellagrous eruption in a black-skinned native child, Dr. Williams says, 'Their distribution and their character remain distinct from the rash that is typical of pellagra.'

Further on it is stated 'the skin at the corners of the mouth and eyes also begins to peel off, leaving raw areas.' Sores on the mucous membrane in the mouth appear and corneal ulcer and photophobia may be noted.

Diarrhoea becomes persistent and pyrexia is present, irritability is marked; death usually ensues in a month or less in untreated cases. No changes in the reflexes were found.

In the case reports some other features are mentioned, ' the skin all over was atrophic in appearance . . . there were darker almost pavemented-like patches on the forearms and legs . . . the typical distribution of pellagra was absent, i.e., the dorsum of the hands and feet seemed to escape until the last stages of the disease.' Stomatitis is mentioned, also purulent discharge from the vagina. Casual mention is made of an older child (4 years) who had had a series of improvements with relapses.

Dr. Williams has described what, to workers with an extensive clinical experience of pellagra, must appear as a complete picture of that disease in young children. The present writer over twenty years ago also failed to recognize pellagra when he came across the disease in Central Africa and described[2] the first group of cases to be recognized in that continent south of Egypt.

In the diagnosis of pellagra allusion is commonly made to the triad of symptoms—dermal, gastro-intestinal and nervous, much stress is laid upon the distribution of the skin lesions, and the seasonal recurrence is a point to which prominence is given. The descriptions in text-books are based upon adult cases and reference is rarely made to the skin manifestations as seen in dark races or to a number of other important points.

In the first place the great variability in the course of the disease must be remembered. In a fulminating case, in which continuous diarrhoea is a prominent symptom, death may ensue after a few weeks' illness. The skin lesions might be overlooked and nervous manifestations unrecognized. On the other hand, the disease may run a very chronic course over many years with intermittent symptoms and the case find its way into an asylum for the insane. In many cases the onset is insidious: in others, apparently after the causes have been at work for some long period of time (this side of the question cannot be discussed here) the onset of ' the attack of pellagra ' is sudden and the course may be rapid. In children there may be a high mortality, while in infants, if unprotected (they usually are protected) the disease may run a course, well exemplified in the Accra infants, resembling infantile beriberi as recorded by George Bray[3]. The order in which systematic symptoms appear may vary, but in the acute cases gastro-intestinal and dermal symptoms are closely associated, though one may precede the other by some short interval as in Dr. Williams' cases. As in her cases so in pellagra the diarrhoea is a simple diarrhoea intermittent at first. It soon becomes persistent, often unaccompanied by pain, and it may be associated with a tendency to vomiting as seen in the Accra infants.

The loss of gloss and colour of the skin and hair mentioned by Dr. Williams as occurring in sick natives and seen in minor degree in her patients is of course well recognized. In many chronic cases of pellagra it may be well marked. Dr. Williams speaks of ' depigmentation ' suggesting that there is actually a removal of the granules of melanin from the skin and hair. This point has nothing specifically to do with pellagra perhaps, but it would be interesting if it could be settled by histological examination. The appearance may be due merely to a draining away from the skin of blood and other tissue fluids.

The actual skin lesions and their evolution as recorded by Dr. Williams are those of pellagra in a dark-skinned race as has been stated above. They are, I venture to say, absolutely diagnostic. In no other condition is found the lesion as described. The black patches noted by Dr. Williams resemble the skin lesions I described as if the area had been painted over with a layer of paint made of lamp-black which then becomes cracked and wrinkled and peels off leaving a pink, sometimes raw surface beneath.

It must not be forgotten however, that the skin lesions in pellagra are variable. On the one hand, the process may be acute with haemorrhage into the skin and necrosis, or the erythema may be mild and followed by a branny desquamation only. On the face the rash may take on an acneiform character; on the shin the skin may be smooth and shiny having the appearance of having been painted over with collodion, to crack later, characteristically giving rise to the ' crazy pavement ' effect, so aptly designated by Dr. Williams.

The distribution of the skin lesions in the West African infants has obviously caused Dr. Williams difficulty. In most text-books the statement is commonly made that the pellagrous rash appears on exposed areas of skin and the reader is led to believe that it can only appear on those parts exposed to sunlight, that in fact the skin is photosensitized and the rash is determined by exposure to the sun's radiations. This is often coupled with another statement to the effect that the skin of the terminal phalanges of the fingers is never affected and that the skin of the palms is likewise exempt.

Sandwith pointed out that the rash was absent from the terminal phalanges of pellagrous Egyptian peasants and demonstrated that this was due to their being hidden from the sun's rays by the handle of their hoes. The statement in regard to the exemption of the phalanges is, however, now repeated by many writers without the explanation, and as such is quite untrue. To say that the palms are never affected in pellagra is also untrue. Certain changes are not uncommon, but they are not the same as those on the dorsum and are overshadowed by the latter.

The pellagrous rash may tend to appear on certain predetermined areas of skin just as happens in the exanthemata, the predisposition being due to certain anatomical and physiological conditions and those areas may correspond to ' exposed areas ' and sunlight may commonly be an exciting cause of the eruption, but the truth should be stated in general terms and is to the effect that any part of the skin in pellagra may be affected and that any form of trauma or irritation may determine the site of the lesions. Any form of radiant energy, any chemical stimulus, any form of physical irritation may, it seems probable, act as an exciting factor, very much as in smallpox for example.

Thus are explained all those more unusual localizations of the pellagrous rash and thus are accounted for the localizations in the African children of Dr. Williams as she herself has shown without realizing the significance of her own acute observations. She noted that the rash appeared at points of pressure and irritation and that the distribution was not the same as is described for adults which after all is what one would expect. The buttocks in some of the infants were affected as may be the case in pellagrous children with diarrhoea, the soiling of the skin being sufficient to determine a pellagrous eruption in this area.

In pellagra other very characteristic signs, as I pointed out many years ago, are the little sodden areas of skin, which appear white in black-skinned races, at the angles of the mouth, at the external canthus of the eye, at the free margin of the prepuce, about the vulva (often associated with a vaginitis) and about the anus. All these, with the exception of the condition about the anus, have been noted by Dr. Williams in her cases. In man a very characteristic change in the skin of the scrotum is often observed. It would be interesting to know if anything of the kind had been seen by Dr. Williams in her male infants.

The stomatitis and ulceration of mucous membrane, again so characteristic of pellagra, were also seen in the Accra infants.

Lastly, in regard to nervous and mental symptoms it may be stated that in pellagra, perhaps the commonest sign referable to the central nervous system is an increased knee-jerk. In a great proportion of cases, where the disease is established, the phenomenon is seen, but just how soon after the beginning of ' an attack ' in infancy this change in patella response occurs I do not know. The absence of any alteration in the reflexes in the rapidly fatal cases among the Accra infants in no way invalidates a diagnosis of pellagra. In annually recurring attacks of pellagra in children there may be no nervous symptoms the first years. Some mental change, too, is common in pellagra apart from the gross changes to be witnessed in severer cases. In children the mental responses are naturally limited in certain directions, that seen in infants is one of irritability. In Dr. Williams' cases this was a characteristic symptom. The fever, absence of severe anaemia, leucocytosis and any characteristic lesion at necropsy in the infant cases are, of course, all part of the picture of pellagra.

Dr. Williams has, I believe, described typical cases of infantile pellagra. When in the title of her communication she states that the syndrome she has recorded is associated with a maize diet she suggests that she believes the disease is due to a maize diet. It is an interesting point: the association of pellagra with maize is centuries old, but the proof that a maize dietary plays any part in producing pellagra is still unconvincing.

In conclusion I would like to suggest in regard to treatment that a trial be given to yeast which I have myself found very efficacious. In the Gold Coast Colony there may be some naturally occurring fermentable juice which could be used, one similar to the ' toddy ' with which Bray[3] saved generations of infants in the Central Pacific Island of Nauru from death with infantile beriberi. Experiment and research would soon demonstrate the possibility of using such a substance and the conditions and precautions necessary in making an active preparation.

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PYELOGRAPHY IN INFANTS

BY

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Pyelography in infants is an examination which is essential under certain circumstances, and from it valuable facts may often be obtained which would be undiscovered without this specialized form of investigation. Hitherto the examination has been surrounded by difficulties of such a nature that it is often unsuccessful and the child is submitted to discomfort without result. The object of this paper is to bring forward certain notes on cases where pyelography has been indicated. The observations from a series of sixteen cases have led to the development of a method whereby good pyelograms have been obtained with certainty.

Instrumental pyelography in infancy is a procedure not to be advised lightheartedly, but there are occasions where the indications are definite and adequate: in these cases the anticipation of possible information to be gained justifies submitting the infants to what constitutes a major examination. In this series are cases of urinary infection resistant to the usual medical treatment, of renal pain, of renal calculi, and cases of congenital malformation of the urinary tract similar to those described by Poynton and Sheldon[1]. The term pyelography is used here for brevity rather than accuracy, for it embraces a complete investigation of the urinary tract, including ureterography.

Methods of pyelography.—The choice lies between intravenous and retrograde or instrumental methods. After consideration of these cases it appears clear that an instrumental pyelogram is preferable for many reasons. In an intravenous pyelogram the shadows obtained are not dense and they may become invisible after the slightest movement of the kidneys with respiration. The interpretation of the intravenous pyelogram is sometimes fallacious, failing to show pathological conditions which are eventually clearly demonstrated by an instrumental pyelogram. In certain cases of congenital deformity of the urinary tract, such as hydro-ureter and hydro-nephrosis, an intravenous pyelogram fails to give any shadow until six hours after injection of the uroselectan and even then quite frequently no shadow is seen. The difficulties of radiography in children are familiar to all and it is clear that a method taking at least three-quarters of an hour is undesirable.

Anaesthesia.—When the instrumental method is employed anaesthesia is essential. Even when instruments cannot be used, as for example in the

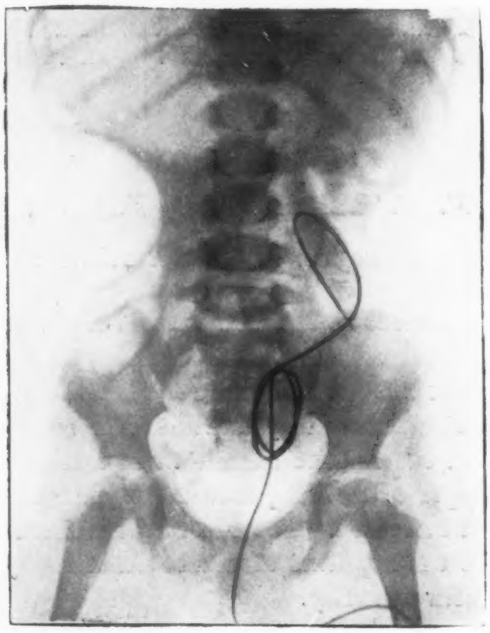

FIG. 1.

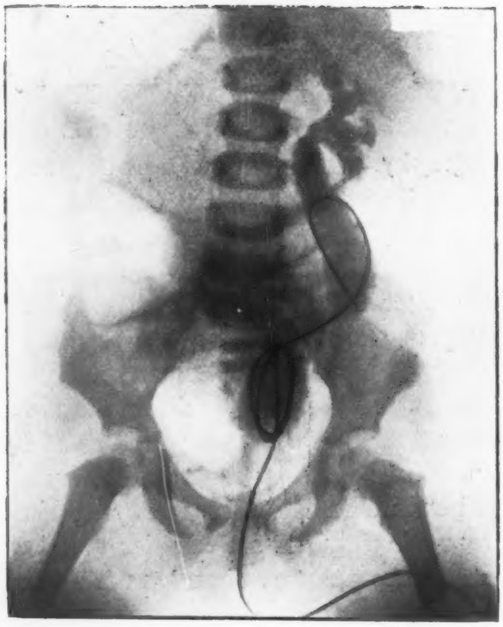

FIG. 2.

case of a male infant with a small external urinary meatus, it is generally preferable to give an anaesthetic for the following reasons:—

(1) Without an anaesthetic it is possible to inject the uroselectan into a vein but the subsequent mental and physical upset results in a blurred pyelogram however short the exposure.

(2) By giving an anaesthetic a satisfactory still pyelogram may be obtained by a method to be described later.

The choice of anaesthetic is important: nitrous oxide and oxygen anaesthesia is adequate and safe, there are no unpleasant after-effects and it can be made to play an important part in the radiographic technique.

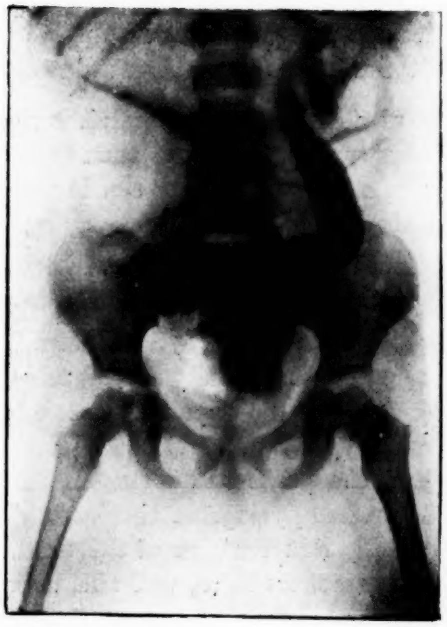

FIG. 3.

Radiographic difficulties have been discussed by Beer and Hyman[2] who state that the youngest child on whom they have carried out double pyelography was two years old. They also say, ‘ Owing to the movement of the infant, all x-ray exposures must be instantaneous and without a Buckey diaphragm at the best it is difficult to obtain perfect pictures with regularity.’ Exposures from half a second upwards are desirable for detail in pyelography using a Buckey diaphragm or a Lysholm grid, otherwise the shorter, so-called instantaneous, exposures of one-tenth of a second must be used which give neither good definition nor, for certainty, still pyelograms.

Instrumental pyelography.—The following method, if well-trained assistants are available, enables the pyelography to be carried out in a very short time. The cystoscope is passed and the interior of the bladder examined; very little time should be spent on this unless some gross abnormality is seen, in which case the knowledge gained by longer examination will repay the time spent. When the ureter or ureters have been catheterised with No. 3 catheters, the bladder is emptied and the cystoscope withdrawn; ureteric catheter specimens of urine may now be collected if this is necessary. After tilting the infant 20 degrees into a Trendelenberg position, the renal regions are examined under the screen to verify the position of the ureteric catheters; the renal pelves are then filled with 20 per cent. sodium bromide solution. It is important that this filling of the renal pelves should be controlled by sight, under the screen, for these reasons: —

(1) The usual way of verifying that the pelves are filled, by the patient experiencing renal pain, is not available in the anaesthetized infant and vision is the only method of ensuring that the pelves are really full.

(2) The capacity of an infant's renal pelvis is normally 2 or 3 c.c. and it would be unwise blindly to inject more than this, yet if an abnormality exists the pelvis may take 5, 10 or even 15 c.c. before being sufficiently filled to give the correct shadow.

It is impossible to obtain true pyelograms without risk of over-distension, unless this be done by direct vision under the screen.

The three uretero-pyelograms Fig. 1, 2 and 3 illustrate this point. They were taken after 5 c.c., 10 c.c. and finally a total of 15 c.c. had been injected on the right side. In this case the opposite pelvis was normal, holding only 2·5 c.c. It was not until the total 15 c.c. had been injected and the ureteric catheter withdrawn that the pelvis and ureter on the right were completely filled and an accurate uretero-pyelogram obtained. The kidney and ureter were infected, nephrectomy and excision of the ureter were performed and the child left hospital two months later, well and with a sterile urine.

Immediately the pelves are filled, the anaesthetic is discontinued and after approximately a minute an x-ray is taken. The infant is placed in the reversed Trendelenberg position, the ureteric catheters are withdrawn while injecting a further 1 c.c. of bromide solution and a skiagram of the filled ureters and renal pelves taken.

The whole difficulty in taking these pyelograms is to secure a period of inhibited respiration sufficiently long to enable the radiographer to make an adequate exposure and it has already been shown that not less than half a second is needed. Previously an exposure of one-fifth of a second was made during quiet respiration in the hope that a still picture would result, and blurred pyelograms were only too familiar.

Fig. 4, 5, 6 represent the experimental record of a pyelography on a child two years old. The respiratory movements were obtained from a rubber bag lightly strapped over the infant's chest and connected with a tambour. The lowest tracing represents a time interval in half seconds; the intermediate line marks the beginning and end of the x-ray exposure. Fig. 4 shows a tracing of quiet shallow respiration under the anaesthetic. It will be seen from this chart that there is insufficient time at any part of the curve to allow an adequate exposure with any chance of obtaining a still pyelogram. Fig. 5 shows the whole series of respirations from the moment the anaesthetic was discontinued at the point X to the point Y where a successful pyelogram

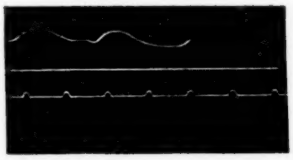

FIG. 4.

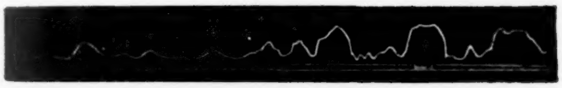

FIG. 5.

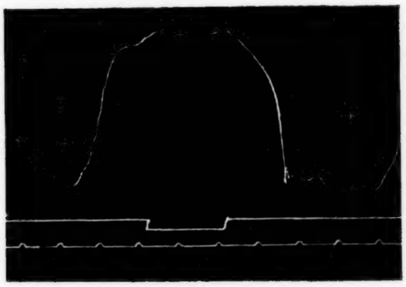

FIG. 6.

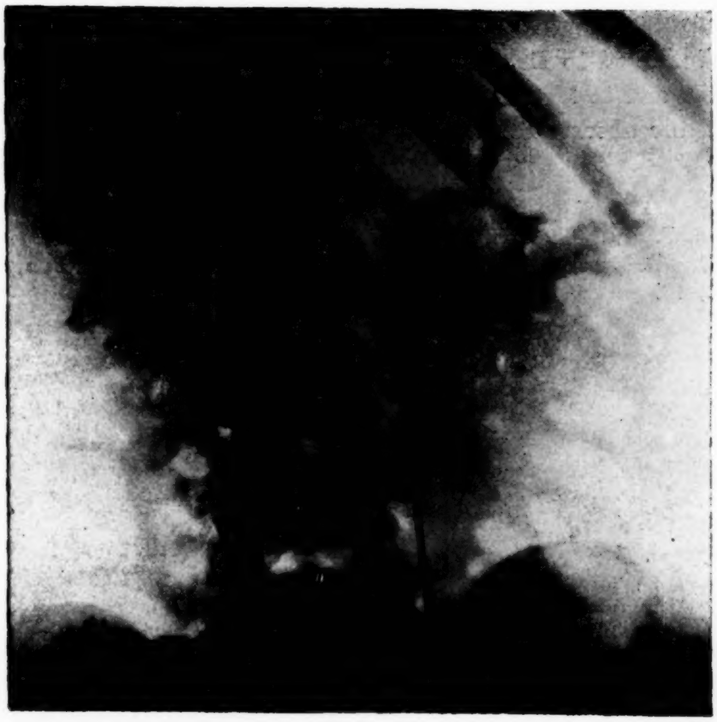

FIG. 7.

NOTE.—In Fig. 5 the tracing on the smoke drum has been broadened for clearness of reproduction, the other tracings were photographed direct from the drum.

had been obtained. The time X Y varies with different infants, the length of anaesthesia and other factors but is in the region of one minute, sometimes being as long as three. It will be seen that there are periods of apnoea followed by intermittent deep inspirations, the inspiration Y being deeper and more sustained, the tracing showing a typical plateau. Fig. 6 shows the point Y on a larger scale where an x-ray exposure of one second was possible during which the diaphragm was absolutely at rest, thus allowing a still and consequently clearly defined pyelogram.

The periods of apnoea often suggest themselves as suitable moments for x-ray exposure, but they are found to be of variable length and the next inspiration may occur unexpectedly. On the other hand, once there occurs the sustained inspiration, which gives the plateau tracing, one can be sure of subsequent similar inspirations during which satisfactory x-ray exposures can be made. This method has now been carried out successfully in the last twelve consecutive cases.

The actual skiagram taken while the observations shown in Fig. 6 were made, appears as Fig. 7.

I am indebted to Dr. Charles Harris for permission to publish some of this material and to Mr. Girling Ball for allowing me to investigate the cases and record the observations.

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UNUSUAL CASE OF DISSEMINATED SARCOMA IN A CHILD

BY

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AND

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A remarkable case of malignant disease in a young child, apparently arising from a growth in the caecum, was recently under our care. The diagnosis during life presented great difficulty and was finally made on the pathological findings at post mortem.

Case report.

The child, at the age of six months, was first brought to the Infants Hospital for treatment for sleeplessness and continuous crying, symptoms which were at the time regarded as due to teething, and treated as such. From that time forward until admission to the hospital on September 1st, 1933, the child attended intermittently at the out-patient department of the hospital for a variety of symptoms—colds, colitis, intestinal disturbances, throat troubles, and other minor ailments. The tonsils were removed by Mr. P. Franklin in August, 1931, when the child was two years of age. On the 29th August, 1933, at the age of four years, he was again brought to the hospital for diarrhoea, threadworms, and a rash on shoulders and arms. On this occasion he was seen by one of the clinical assistants, but no note was made of the size of the liver, although there is mention that the abdomen was enlarged. On September 1st, 1933, the child was again brought to the hospital with a note from Dr. S. E. Knowles, of New Cross, calling attention to the size of the abdomen and the difficulty in breathing. He suggested that the case might be one of tuberculosis. The child was then admitted to the hospital as an in-patient.

On examination it was found that the liver was enormously enlarged, extending almost to the umbilicus. It was uniformly smooth and not hard. Nothing else could be discovered in the abdomen to account for the general enlargement. There was no free fluid, no tumour, and no obvious distension of the intestines. The child's breathing was rapid and laboured, and on the second day after admission the temperature rose, together with the respiration and pulse rate. During the fourteen days which intervened between the date of admission and the child's death, the general condition rapidly grew worse, with general rise in temperature, pulse rate, and respirations. There was a very profuse perspiration, and a rash broke out on the face, which at first was regarded as sordes, but later on as an unusual form of tuberculide.

The physical signs of the chest were somewhat indefinite, and hardly sufficient to account for the dyspnoea and respiratory distress, but clinical evidence of double pleuritic effusion with collapse of lung at both bases gradually developed, and was confirmed on September 4th by X-ray examination.

Although the symptoms and general condition of the child on the whole favoured a diagnosis of tuberculosis, the condition of the liver and the rapid down-hill course of the child left us in considerable doubt as to whether there was not some other interpretation.

The urinary report threw little light on the case, but acetone and a trace of diacetic acid and urates were found to be present. A blood examination showed a high degree of acidosis. The throat and nasal swabs gave negative results for K.L.B. The differential blood count was as follows:—erythrocytes 5,375,000, haemoglobin 112 per cent., colour index 1·04, leucocytes 7,200.

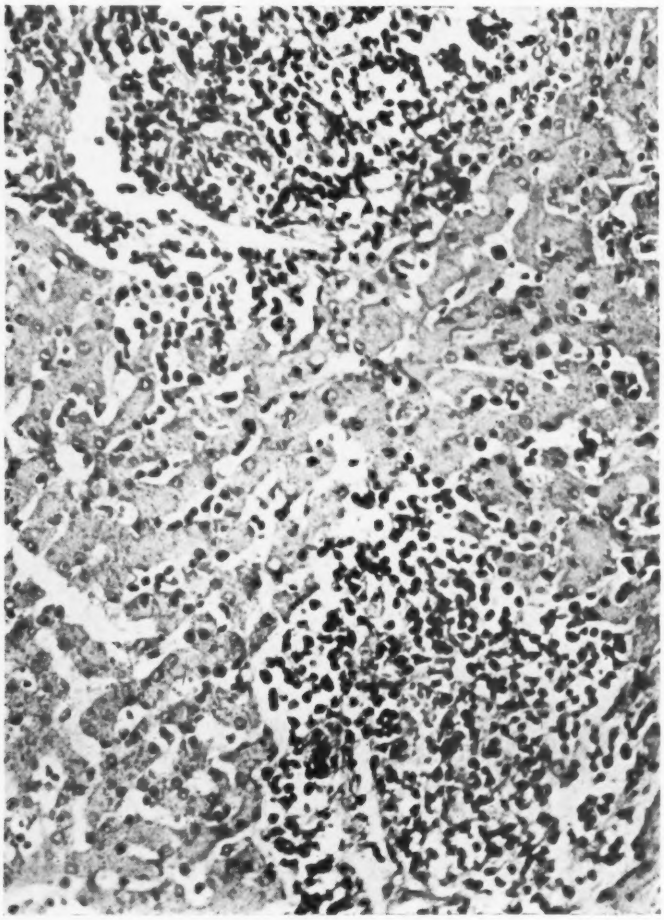

FIG. 1.—Section of liver showing the neoplastic invasion.

Differential count:—polymorphs 47·2 per cent., eosinophils 2·4 per cent., neutrophil myelocytes 10·4 per cent., basophils 0·4 per cent., large hyaline cells 1·2 per cent., lymphocytes 37·2 per cent. One normoblast seen in counting 250 cells—*i.e.*, 29 per c.mm., erythrocytes otherwise normal. Mean diameter of erythrocytes (Eve's method) 7·30 microns. No tubercle bacilli were discovered in faeces, or urine, after the employment of both direct and concentration methods. The skin reaction was positive to human, but negative to bovine tuberculin.

On the 13th day after admission, the dyspnoea becoming worse, the right side of the chest was aspirated, and 5 c.c. of blood stained fluid was withdrawn. In this there was a rather heavy coagulum, with a considerable number of white cells, mainly lymphocytes; no organisms could be discovered by direct examination, and only one colony grew on culture. This was found to be staphylococcus aureus, and was probably a contamination. The fluid was inoculated into a guinea-pig with negative result.

From this time forward, the child went rapidly down-hill, with delirium at times, but with no definite meningeal symptoms.

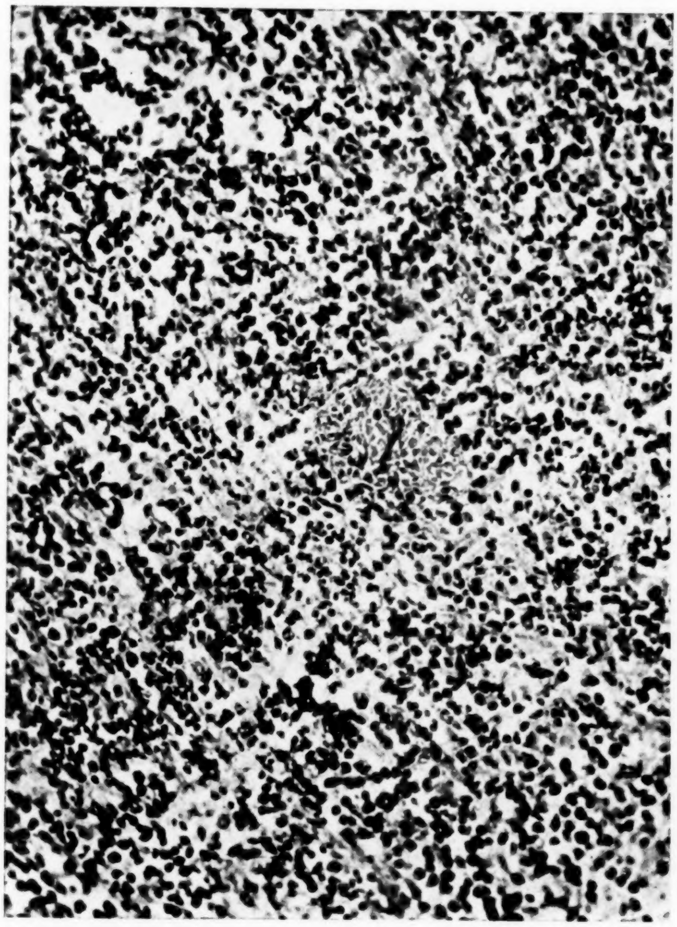

FIG. 2.—Section of spleen, showing great destruction of normal architecture.

Discussion.

The clinical interest in this case lay chiefly in the difficulty of making a definite diagnosis during life. There was some evidence that the case might be one of tuberculosis, and yet the general clinical picture was not entirely in accordance with this view. The uniform and extensive enlargement of the liver was not altogether suggestive of either tuberculosis or of a neoplasm, and with the exception of a few pedunculated excrescences on the skin, we could find no evidence of primary or secondary growth. We had intended to excise one of these and submit it to microscopical examination, but the child died before this investigation could be carried out.

Although the post-mortem pathological report which follows shows clearly that this case was one of a very widely disseminated malignant growth, with the exception of the pedunculated excrescences on the skin referred to above and the somewhat unusual differential blood count, there was little evidence to justify a diagnosis of malignant disease. It is interesting to note that throughout the case there runs a connected history of bowel disturbances, which inclines us to the belief that the primary growth may possibly have been in the caecum. The co-existence of tuberculosis is probably an unimportant event in the history.

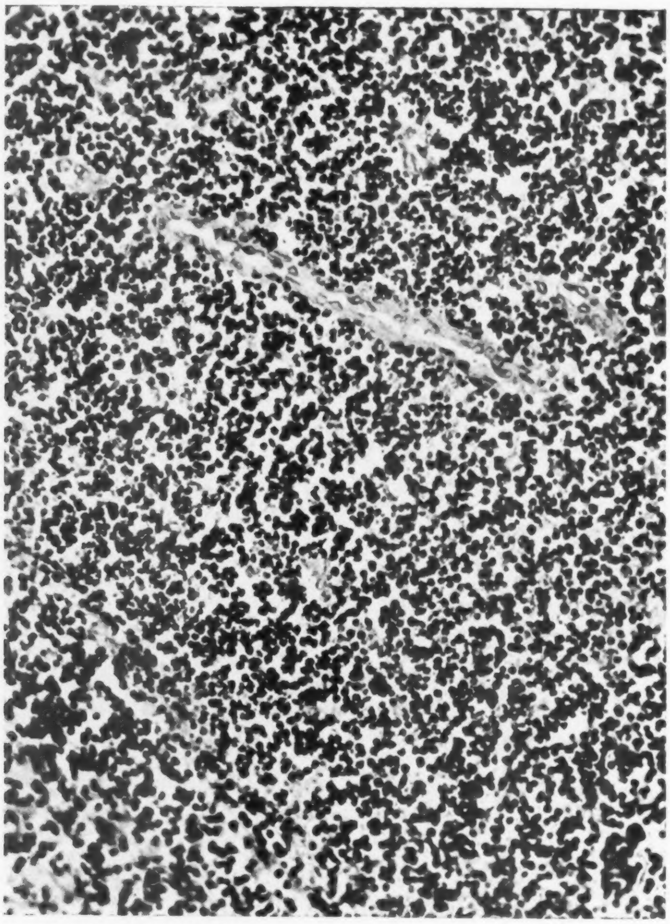

FIG. 3.—Section of tumour of the caecum (the possible primary lesion).

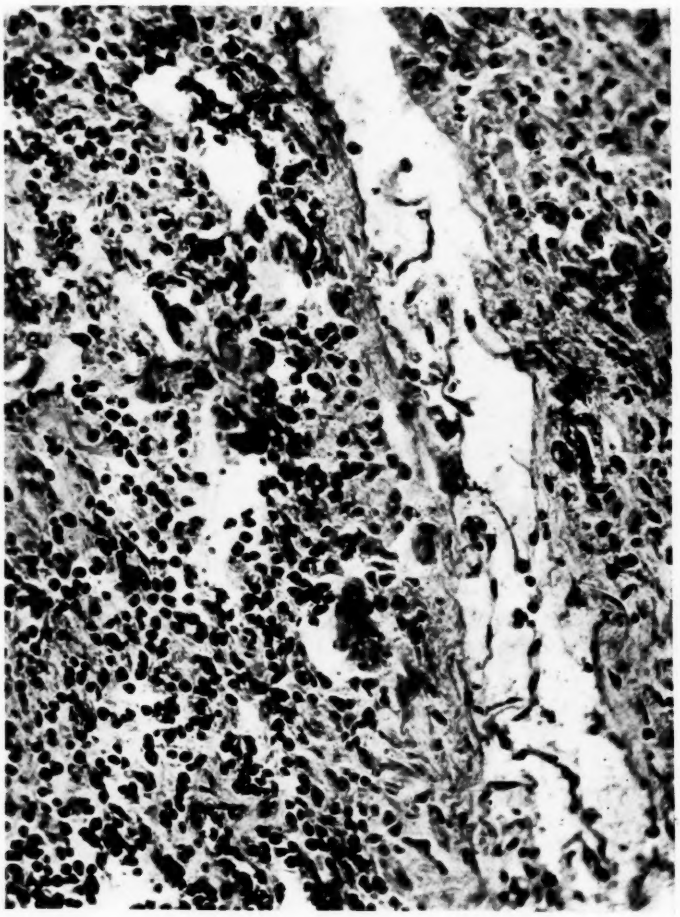

FIG. 4.—Section of gall bladder, showing destruction of normal tissue.

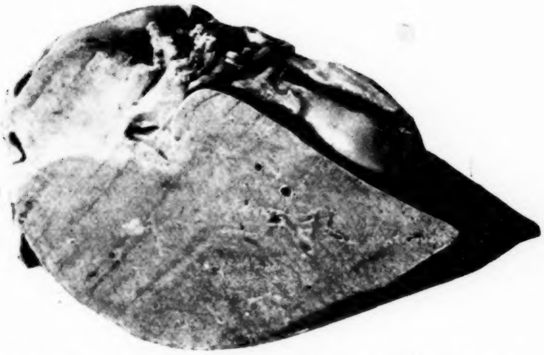

FIG. 5.—Macroscopical view of liver with gall bladder in situ.

Pathological report (post mortem).

Very wasted male child with excessive labial sordes. Many small reddish pedunculated lesions of skin present. Abdomen markedly distended. Rigor mortis passing off. Post-mortem staining well seen.

ALIMENTARY SYSTEM. Mouth, pharynx, oesophagus, stomach, duodenum, and jejunum, normal. The ileum showed marked hypertrophy of Peyer's patches. Minute intramural tumour-like lesions were present along the longitudinal axis of the caecum with some superficial ulceration. The large intestine was distended. The appendix was thickened, directed upwards and adherent to the right suprarenal capsule. A large white ' cauliflower ' tumour (see illustrations), occupied the whole of the posterio-inferior aspect of the caecum, but did not obstruct the opening of the ileo-caecal valve. The whole of the bowel in this region was studded with minute neoplastic growths with superficial ulceration. The mesenteric lymph nodes were large, hard, discrete, mostly showing definite haemorrhages on section. The intestines contained much foul-smelling and altered blood.

THE LIVER was very large, weighing 1,210 gm. (normal for age, 500 gm.). The edges were rounded and the capsule thickened, with numerous subcapsular deposits varying in size from a hemp seed to a lentil. On section, the liver was studded with innumerable white infiltrations in the interlobular regions. The gall bladder deserves special comment. Before opening it appeared completely solid, and on section was found to have greatly thickened walls, and to be devoid of bile, but containing some clear mucus in the fundus. The bile ducts were normal and patent.

CARDIOVASCULAR SYSTEM. The pericardium was normal, with no effusion. The heart was small and the valves and great vessels normal. The muscle was friable and pale.

RESPIRATORY SYSTEM. The larynx was normal. There was some muco-pus in trachea. The parietal pleura was beset with numerous flat white nodules running in intercostal grooves, more marked on the right side. The right pleural cavity contained 600 c.c. and the left 250 c.c. of blood stained serous fluid with fine coagula. The diaphragmatic pleura was beset with nodules similar to above, but the visceral pleura was free from nodules. The right lung collapsed. One hilar lymph node was enlarged to size of walnut, caseous and blocking the bronchus, but showing no ulceration. Tubercle bacilli were demonstrable in stained sections and direct films. The left lung was only partially collapsed. No caseation of hilar nodes present. No deposits found in or on lung surfaces. The mediastinal lymph nodes were greatly enlarged, hard, discrete, mottled and firm on section.

GENITO-URINARY SYSTEM. Both kidneys were fatty, pale, and studded throughout their substance with multiple miliary circumscribed haemorrhagic and necrotic areas. The ureters and bladder were normal and the testes normal.

DUCTLESS GLANDS. The spleen weighed 350 gm. and was large, hard and studded throughout with white deposits similar to those in liver. The left suprarenal capsule was normal. The right appeared large and involved in a mass of whitish material anchoring it to the kidney, appendix, and right side of diaphragm. One small circumscried and partly haemorrhagic nodule was found in the usual site at apex of capsule. The thymus, thyroid, pituitary, and pineal glands were apparently normal.

LYMPHATIC GLANDS. The axillary, inguinal, and cervical glands were all hard, discrete and grey-white in colour.

THE SKULL was normal and the brain was normal. The ears did not contain pus.

SKIN TUMOURS. These varied in size from lentil to filbert and were pedunculated, red-purple, and showed early ulceration. They were distributed in a linear fashion on the face and back, particularly over sacral region.

Histological investigation.—Sections were taken of a skin tumour, the liver, spleen, kidney, tumour of caecum, right suprarenal, mass from coeliac axis, gall bladder, lymph node from coeliac region, hilar lymph node (caseous), and a mesenteric lymph node.

All these sections were stained with haematoxylin and eosin, and, in addition, were examined by Schmorl's method for acid fast bacilli and by Gram's method for micro-organisms. Acid fast bacilli were found only in sections from the hilar lymph node, Gram positive cocci were seen in the skin tumour only. The remaining sections showed various degrees of destruction of normal tissue and replacement by neoplastic cell growth. The invading tissue was of fine alveolar structure and composed mainly of small round cells with a deeply staining cytoplasm, the nuclei of which showed varying degrees of nuclear mitosis. There were also large blood spaces of irregular type and there was no attempt at reproduction of tissue form. In other words, the condition was one of a widely disseminated invasive round-celled sarcoma. With regard to the primary tumour, it is possible, but not conclusively demonstrable, that the original growth was in the caecum, and that the condition present was a wide dissemination from this primary focus. On the other hand, from the abnormal blood picture, the generalized enlargement of the lymphatic glands, and wide distribution of the lesions, the inference is that we were here dealing with an abnormal border-line case between sarcomatosis of a diffuse type and the aleukaemic stage of a myelogenous leukaemia.

The investigations performed during life were carried out as routine investigations and the findings were considered to point to an unusual reaction to a generalizing tuberculosis. There was at no time any clinical indication that the post-mortem findings would take the above described form.

At the autopsy itself we were still left with the choice of several alternative diagnoses, and of these the following seemed the more probable:—

(a) Generalized tuberculosis of the hypertrophic granulomatous type.
(b) An atypical Hodgkin's disease.
(c) Malignant disease of hypernephromatous or sarcomatous type.

The actual diagnosis rests on the histological examinations subsequently carried out, some of the more typical of which are illustrated by microphotographs (Fig. 1 to 4: magnified 360 diameters) taken by Mr. J. G. Bradbury, F.R.M.S., F.R.P.S.

From the post-mortem findings it will be seen that there was some justification for our failure to arrive at a correct diagnosis during life.